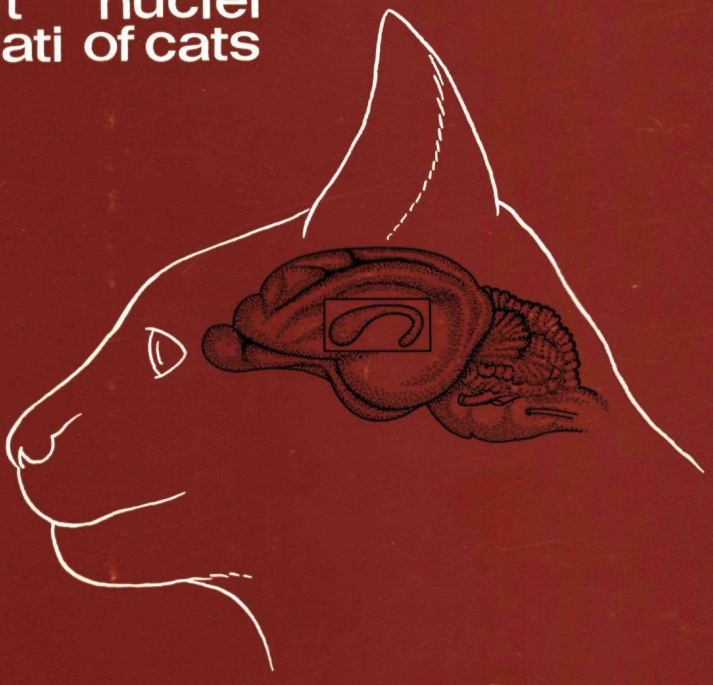
the caudate nucleus and neurochemical control of behaviour

the function of dopamine and serotonin in the caput nuclei caudati of cats



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THE CAUDATE NUCLEUS AND NEUROCHEMICAL CONTROL OF BEHAVIOUR

THE FUNCTION OF DOPAMINE AND SEROTONIN IN THE CAPUT NUCLEI CAUDATI OF CATS

PROMOTORES

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THE CAUDATE NUCLEUS AND NEUROCHEMICAL CONTROL OF BEHAVIOUR

THE FUNCTION OF DOPAMINE AND SEROTONIN IN THE CAPUT NUCLEI CAUDATI OF CATS

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE
WISKUNDE EN NATUURWETENSCHAPPEN
AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF MR F J F M DUYNSTEE
VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN
IN HET OPENBAAR TE VERDEDIGEN OP
WOENSDAG 20 JUNI 1973 DES NAMIDDAGS TE 4 00 UUR

DOOR

ALEXANDER RUDOLF COOLS

GEBOREN TE DEN HAAG

DRUKKERIJ BRAKKENSTEIN NIJMEGEN THE NETHERLANDS
1973

The present dissertation is based upon the following papers

Cools, A R and Rossum van, J M Caudate dopamine and stereotyped behaviour of cats *Arch Int Pharmacodyn Ther 197, 163 (1970)*

Cools, A R The function of dopamine and its antagonism in the caudate nucleus of cats in relation to the stereotyped behaviour *Arch Int Pharmacodyn Ther 194, 259 (1971)*

Cools, A R Athetoid and choreiform hyperkinesias produced by caudate application of dopamine in cats *Psychopharmacologia 25, 229 (1972)*

Cools, A R Chemical and electrical stimulation of the caudate nucleus in freely moving cats the role of dopamine *Brain Res (in press)*

Cools, A R Serotonin a behaviourally active compound in the caudate nucleus of cats *J Israeli Med Sci (in press)*

Cools, A R Chemical and electrical stimulation of the caudate nucleus in freely moving cats the role of serotonin *(submitted for publication)*

Cools, A R The transneuronal relationship between dopamine and serotonin in the caudate nucleus of cats *(submitted for publication)*

ACKNOWLEDGEMENT

The author is greatly indebted to all persons who contributed to the realization of this study Thanks are expressed to the staffs of the Pharmacological Department and the Department for Comparative and Physiological Psychology for friendship, support and valuable discussions
The author whishes to thank Mr W A F van Amerom, Mr S C M Dicker, Mrs C J C de Groot-Versteegden, Mr G Hendriks, Mr W Hoeboer, Mr J A L Janssen and Mr P Lambrechts for their technical assistance, Dr A H M Lohman for his great help and expert advise in designing the anatomical drawings, Drs W M J Raaymakers for his interest, enthusiasm and valuable suggestions, Mr E de Graaf and co-workers for their important bibliographic aid, Mr J J M de Bekker, Mr C P Nicolasen and Mr E F W Noyons for drawing the excellent figures, the whole staff of the Medical Illustration Department for photographic aid, the whole staff of the Central Animal Laboratory for taking care of the animals, the whole staff of the Technical Centre for constructing mechanical devices, Miss J A Th M Hurkmans for her invaluable assistance in many respects, Drs C L M Broekkamp, Drs A J J Pijnenburg, Dr F Seutter-Berlage, Miss A M Simonis, Drs H A J Struyker-Boudier and Drs C C B Wijffels for their helpful advise and constructive criticisms in the preparation of the manuscript, Dr D W K Cotton for polishing the english text, and many others for their more incidental assistance and remarks
Thanks are also due to Dr J M Kemp and Brain Research for permission to reproduce fig 6 in chapter 2 2 3, and the UCLA Brain Information Service for basic sciences bibliographic services in the field of "biogenic amines and transmitters in the nervous system"
The investigations were supported in part by grants from the Netherlands' Organization for the Advancement of Pure Research (ZWO)

The investigations were carried out in part in the Institute of Pharmacology, and in part in the Institute of Psychology, University of Nijmegen, The Netherlands

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neostriatum refers to the caudate nucleus and putamen as opposed to the paleostriatum, i e. globus pallidus; it also refers to structures homologous with both nuclei together, e g. the caudate-putamen complex in rats.

stereotypy refers to abnormal behavioural patterns, marked by monotonous repetition of discrete types of behaviour, normally occurring in association with other types of behaviour. The term stereotypy in this dissertation denotes the abnormal behaviour induced by intraperitoneal injections of dexamphetamine, its close analogues and apomorphine

"contralateral" and "ipsilateral" syndromes refer to syndromes, marked by unilateral turning movements of the head and unilateral non-patterned movements of the forelimb, often accompanied by discrete contractions of various muscle groups. these movements and/or contractions may mainly occur on the side of the injection (ipsilateral) or on the side opposite to that of the injection (contralateral).

hyperkinesias refers to the excessive appearance of locomotor patterns, such as walking and climbing, in animals which show normal orienting-responses.

hyperreactivity refers to the excessive appearance of locomotor patterns, such as walking and climbing, in animals which show increased orienting-responses.

"vacuum" activities refers to the performance of patterned activities, such as eating and prey-catching, despite the absence of appriopriate, exteroceptive, stimulation

athetosis refers to repetitive involuntary, slow, gross movements (see also: Denny-Brown, D In. The basal ganglia and their relation to disorders of movements *London, Oxford University Press (1962))*

chorea refers to irregular involuntary, fast, gross movements (see also: Mettler, F. A. In· Neurophysiological basis of normal and abnormal motor activities. *(Yahr, M. D. and Purpura, D. P. eds), New York, Raven Press, 472 (1967)).*

hypokinesia refers to a general paucity of movements.

CHAPTER 1

SCOPE AND INTENT

1 1 INTRODUCTION

In recent concepts dealing with psychomotor diseases in man, the role of neurotransmitters occupies a central role Both in Parkinson's disease and in some spontaneously occurring or experimentally induced psychoses, it appears that the brain dopamine mechanism is involved

During the last decades, evidence was accumulated that the beneficient and, sometimes, unwanted effects of psychoactive agents in the treatment of these diseases, originate from their capacity to interfere with central neurotransmission processes

The search for a pharmacological treatment of Parkinson's disease has led to the discovery that L-3,4-dihydroxyphenylalanine (L-DOPA), which increases the activity of the brain dopamine mechanism, not only ameliorates some motor disorders, but also produces psychological side-effects On the other hand, concurrent research in medical practice has revealed that neuroleptics such as haloperidol, which are believed to inhibit the brain dopamine mechanism, not only ameliorate certain forms of schizophrenia and some aspects of experimental psychoses induced by the dopamine-stimulating agent dexamphetamine, but also result in the elicitation of parkinsonian-like side-effects Despite the enthusiasm about the clinical application of these substances, it appears that the physicians are too often confronted with treatment failures The relative lack of success in the treatment of both motor and psychological disorders has created an urgent need for further basic investigations in the neurochemical control of behaviour

As the limited effectiveness of the pharmacological treatment of some psychomotor diseases in man has focused our interest on the relationship between specific biochemical substrates in the brain and specific forms of behaviour, the relevant data in this field will first be reviewed and then the aim of this thesis will be outlined

1 1 1 THE TREATMENT OF PARKINSON S DISEASE

A number of clinico-pathological studies have revealed that symptoms occurring in the Parkinson's disease such as tremor, rigidity, hypokinesia, rigidity in thinking, lack of creativity, disorientation, deficiencies in recent memory and disturbances in the so-called "Subjekt-Umwelt" relation are accompanied by severe lesions in the caudate nucleus and related nuclei (for reviews Barbeau et al , 1965, Calne, 1970, Cooper, 1969, Korten, 1969, Martin,

1967) Post-mortem investigations of such patients have shown that the histopathological conditions are often combined with a strong reduction in the dopamine content of particular areas of the brain, especially of the substantia nigra, the caudate nucleus and the putamen (for reviews Calne, 1970, Hornykiewicz, 1966, Klawans, 1968, Klawans et al , 1970) At about the same time, it was established that precisely these parts of the brain are normally loaded with dopamine (Bertler et al , 1959, Carlsson, 1959, Ehringer et al , 1960) It is well known that the clinico-neuropharmacological research stimulated by these findings has led to the idea that an increase in the brain dopamine content should have therapeutical effects As dopamine itself does not pass the "blood-brain barrier", the use of L-3,4-dihydroxyphenylalanine (L-DOPA, the precursor of dopamine) which may somewhat easier pass this barrier was suggested The results with L-DOPA treatment were frequently conflicting until it was demonstrated that very large doses were required (for review Barbeau, 1969) Later on, it was found that the combination of L-DOPA and a peripheral L-amino-acid decarboxylase inhibitor is more effective than L-DOPA alone (Birkmayer et al , 1967), this is due to the fact that such an inhibitor blocks the amino-acid decarboxylase both in the periphery and in the walls of the brain blood capillaries so that not only a larger amount of the given L-DOPA reaches the brain, but also a larger amount of L-DOPA is converted into dopamine within the nervous structure itself (Bertler et al , 1964) Today, an enormous list of articles, reviews and books are devoted to studies dealing with L-DOPA treatment and its effectiveness (for reviews Barbeau et al , 1969, Calne, 1970, Crane et al , 1969, Klawans, 1968, Klawans et al , 1970, Papeschi, 1972) The most important outcome of these studies is that, indeed, L-DOPA treatment may result in the improvement of some motor disorders in a number of patients, but that this treatment may also elicit a number of unwanted side-effects such as bucco-lingual-facial dyskinesia, dyskinesia of the upper and lower extremities and psychological disturbances Although it is still an open question whether the L-DOPA-induced psychological side-effects such as anxiety, depression, paranoia, deliria and schizophrenic-like status are "unmasked" disorders or real L-DOPA effects, it is of importance to mention that L-DOPA itself, or one of its metabolites, mediates these effects, since reduction of the L-DOPA dose results in the disappearance of these psychological side-effects (Schwab, 1969)

Both these clinical findings, the finding that the combination of L-DOPA and a peripheral L-amino-acid decarboxylase inhibitor given to animals leads to a significant increase in the dopamine content of the caudate nucleus (Pletscher, 1969), and the finding that the caudate nucleus is normally loaded with dopamine, have raised questions concerning the neurochemical control of this nucleus A more fundamental study of the involved mechanisms may contribute to a better understanding of the L-DOPA treatment failures in Parkinson's disease

Biological research has indicated that schizophrenia is a heterogeneous complex of pathological conditions, each of which may have a different etiology Apart from this difficulty, the picture is further complicated by the lack of any uniform definition of schizophrenia, as Grinker (1969) reports

> "It is likely that in the last one hundred years more investigators have spent more time, money, and energy and written more on schizophrenia than on all other psychiatric problems combined Yet our ignorance concerning its definition, causes, course, treatments, and outcome is still abysmal"

Despite these difficulties, some consistency in the diagnosis is observed disorders of thinking and association including hallucinations, disorders of emotional regulation and disorders of perception are common to most diagnoses (Richter, 1970)

A number of hypotheses about the origin of these schizophrenic symptoms have been postulated To date, most of these hypotheses have been based upon claims, none of which can so far be regarded as firmly based (for review Weil-Malherbe et al , 1971) In general, two main biological research strategies have been employed detection of biochemical abnormalities between schizophrenics and controls, and biochemical analyses of experimental psychoses It is remarkable that relatively little attention has been paid to the therapeutically effective agents and their mechanisms of action in these mental disturbances

Since Delay et al (1952) have reported that phenothiazines are therapeutically effective in certain forms of schizophrenia, a large number of major tranquilizers or so-called neuroleptics, have been tested Today, three classes of neuroleptics are available phenothiazines (prototype chlorpromazine), reserpine-like agents (prototype reserpine), and butyrophenones (prototype haloperidol) Although an account of the qualitative and quantitative differences in the clinical effectiveness of these substances goes beyond the scope of this introduction, it is worthy of mention that the most potent neuroleptics known are 4-(di)phenylbutylamine derivatives such as haloperidol, spiroperidol, pimozide and fluspirilene

In general, neuroleptics are capable of alleviating both acute and chronic psychotic states, although they are less effective in the treatment of affective disorders such as the "unipolar" psychosis in endogenous depression (Cole, 1968, Weil-Malherbe et al , 1971) On the other hand, neuroleptics elicit a number of severe motor side-effects, either during long-term treatment or during the period following the discontinuation of such a treatment, these effects include tremor, choreo-athetoid movements of the limbs, tics and

stereotyped movements such as rocking and lip smacking (Degkwitz, 1969) A number of investigations have indicated that neuroleptics interfere with the brain dopamine mechanism (a) neuroleptics block several characteristic effects elicited by the activation of brain dopamine mechanisms vomiting (Bhargava et al , 1963), stereotyped behaviour (Janssen et al , 1965), suppression of lactation and pseudopregnancy (Kanematsu et al , 1963, van Maanen et al , 1968), and induction of ovulation (Barraclough et al , 1957), (b) neuroleptics significantly increase the turnover of dopamine (Anden et al , 1964, Carlsson et al , 1963), (c) when neuroleptics are intraperitoneally injected in animals, they are mainly stored in dopamine-rich areas (Janssen, 1968), and (d) characteristic pharmacological properties of neuroleptics such as inhibition of self-stimulation and avoidance responses, the abolition of dexamphetamine-induced stereotypies, and the production of ptosis and catalepsy, are reproduced by lesions of dopamine-containing structures (Dresse, 1967) From such data, it has been postulated that neuroleptics block the central dopamine mechanisms at the level of the dopamine-sensitive sites (van Rossum, 1967) In this context, it is worthy of mention that neuroleptics also alleviate some aspects of the experimental psychoses produced by the intake of large doses of dexamphetamine (Angrist et al , 1970) In man, it has been demonstrated that dexamphetamine has at least two conspicuous effects upon behaviour clear-cut psychological effects and characteristic disorders of the patterning of complex movements (Angrist et al , 1971, Randrup et al , 1967, Rylander, 1971) It has been shown that the psychological disorders are remarkably similar to those occurring in some schizophrenic patients (Randrup et al , 1972) As several investigations have indicated that dexamphetamine interferes with brain dopamine (see 2 4 1 2), it appears that the brain dopamine mechanism is also involved in the elicitation of dexamphetamine-induced psychoses Therefore, it will be clear that extension of our basic knowledge about the function of dopamine-rich structures in the brain may also contribute to a better understanding of certain functional and experimental schizophrenic-like psychoses in man

1 1 3 THE BRAIN DOPAMINE SYSTEMS

Since the discovery of the rather specific biochemical topography of dopamine within the brain, many investigators have studied its precise localization and distribution According to our current knowledge, dopamine nerve terminals are concentrated in (a) the neostriatum (the caudate nucleus and putamen), (b) the nucleus accumbens, (c) the tuberculum olfactorium, and (d) the external layer of the median eminence (Fuxe et al , 1967) Of the whole brain dopamine concentration, about 80% is retained in the neostriatum (Bertler et al , 1959) Furthermore, it has been established that the terminals in different anatomical areas belong to at least three different neuron systems the nigro-

neostriatal system, the mesolimbic system, and the tubero-infundibular system (Fuxe et al , 1967)

At the present time, experimental studies dealing with the effects of systemically administered drugs interfering with the metabolism, uptake, release and physiological activity of brain dopamine have indicated that brain dopamine fulfils an important role in the regulation of the pituitary hormones and in the elicitation of stereotyped behaviour With respect to the role of dopamine in the regulation of pituitary hormones, there is some evidence that the so-called tubero-infundibular system is involved (Coppola, 1965, Donoso et al , 1967, Donoso et al , 1968, Kamberi et al , 1969) The terminals of this system make contact with neurons containing luteotropin releasing factors (LRF), and biochemical and histochemical analyses have shown that dopamine released in this area inhibits the activity of LRF during pregnancy (Fuxe et al , 1969, Fuxe et al , 1970) With respect to the role of dopamine in the elicitation of stereotyped behaviour, a central position is assigned to the nigro-neostriatal system (see 2 4 1) The above-mentioned clinico-pathological data have indicated that the neostriatum, in which the largest amount of the dopamine-rich neurons terminate, is probably involved in both motor and psychological disturbances in man Therefore the present investigations will deal with this part of the brain

1 2 THE AIM OF THE INVESTIGATIONS

A number of studies using the classical methods of electrical stimulation and electrocoagulation have indicated that the caudate nucleus has an important influence on the regulation of posture, simple movements and more complex behavioural activities (see 2 1) The anatomical-physiological basis of these functions, however, is far from clear This is due partly to the relatively unknown infrastructure of this nucleus, the highly complex anatomy of its connections, the complex neurophysiological properties of the involved pathways, and partly to the difficulty in ascertaining whether the evoked responses originate in the target area (because of possible spread of the current or destruction of fibres passing through the area, see 2 1 and 2 2) As mentioned in section 2 3 , the caudate nucleus is loaded with dopamine, acetylcholine and, to a lesser extent, with serotonin, gamma-amino-butyric acid and other substances, some of these compounds are believed to be neurotransmitters It is generally accepted that neurotransmitters mediate the transmission of impulses between nerve fibres In fact, the neurotransmission processes within a particular brain structure are essential prerequisites for the transmission of information within that structure, i e its physiological activity In view of the fact that both dopamine and serotonin are restricted to nerve terminals originating from distinct, afferent caudate fibre systems (see 2 3), chemically selective stimulation of the sensitive sites involved can be regarded as an important tool for investigating some aspects of the anatomical-physiological basis of the caudate functions As it is so far unknown whether cholinergic fibres within the caudate nucleus are intrinsic, extrinsic or both, chemical stimulation of this system is less informative in this respect The purpose of the present investigations, therefore, was to study the role of dopamine and serotonin in the neurochemical control of the behavioural functions of the caudate nucleus in order to elucidate some aspects of the anatomical-physiological basis of its functions, and to throw some new light on the functions themselves

The complexity of the distribution of systemically administered drugs have promoted studies dealing with intracerebrally administered drugs Despite the increased interest in the behavioural effects of neostriatally administered substances, our knowledge in this field is relatively scanty (see 2 4) At least two reasons for the lack of success in this research-field can be suggested First, only rats have been used As the neostriatum of rats is an indistinguishable mixture of the 'caudate nucleus" and the "putamen", direct chemical stimulation must have always affected a large part of this complex In view of the fact that there are two different, opposing, functional systems within the caudate-putamen complex of rats (Neill et al , 1970), simultaneous activation or inhibition of both systems could have counterbalanced possible effects The use of animals in which the partition between these nuclei is more

distinct may overcome these difficulties. In the present studies, therefore, the cat brain has been chosen as the test-object· apart from the clear partition between the caudate nucleus and the putamen, the large dimension of the caudate nucleus itself is advantageous because of the possibility of detecting regional effects even within this nucleus

Another reason for the lack of success in studies dealing with neostriatally administered compounds could have been the limited attention given to the elicited effects· the usual practice has been to record the occurrence of "abnormal" behaviour without taking into account changes occurring in "normal" behaviour. Hence the studies done in the past could have offered material too rough for observing changes in this respect. In the present studies, therefore, a more refined recording method has been applied

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CHAPTER 2

REVIEW OF LITERATURE PERTAINING TO THE CAUDATE NUCLEUS

2 1 FUNCTIONAL ASPECTS

In general, there are many levels of description of brain function varying from single cell activity to behaviour As the present study is mainly concerned with motor behaviour, the account given below will be largely restricted to the relevant data within this field, more complex functions as revealed by experiments dealing with conditioned instrumental responses will be discussed in more detail in chapter 6

2 1 1 REGULATION OF POSTURE AND SIMPLE MOVEMENTS

The first step on the road to the behavioural function of the caudate nucleus was made by clinico-pathologists (for review Laursen, 1963) Since James Parkinson published his famous "essay on the shaking palsy" in 1817, a number of clinico-pathological studies in man have indicated that severe motor disturbances such as Wilson's disease, dystonia musculorum deformans, Huntington's chorea and Parkinson's disease are often accompanied by lesions in the caudate nucleus and related nuclei for instance, disorders of postural fixation and equilibrium, righting, locomotion and muscle tone observed in parkinsonian patients, are often accompanied by lesions in the caudate nucleus, putamen, substantia nigra and, sometimes, cortical nuclei (for review Cooper, 1969, Denny-Brown, 1968, Martin, 1967), another example is Huntington's chorea, in which lesions are often restricted to the caudate nucleus (for review Klawans, 1970, Klawans et al , 1971) In general, the pathological conditions in patients with destruction of the caudate nucleus and related nuclei are clinically marked by characteristic disturbances of normal control of movement and posture These data have been interpreted to indicate a motor function of these nuclei (for review Denny-Brown, 1962, Jung et al , 1960, Laursen, 1963, Ward, 1967)

More conclusive evidence in favour of the motor function of these nuclei, especially of the caudate nucleus, has been derived from experimental studies in which either electrical stimulation or lesion techniques have been employed As the results of these experimental studies have been extensively reviewed by Dieckmann et al (1968) and Laursen (1963), only the major points will be mentioned here

Generally, the effects elicited by electrical stimulation of the caudate nucleus are dependent on the frequency and intensity used (cats Buchwald et al , 1961b) Low frequency stimulation, for instance, results in the so-called inactivation syndrome accompanied by raising of the overall threshold for external stimuli, ptosis, miosis, low respiration rate, contralateral turning movements and abnormal positions of the limbs (cats Akert et al , 1951, see also Dieckmann et al , 1968), while high frequency stimulation results in the appearance of strong motor responses contralateral circling, contralateral turning of the head and movements of the contralateral limbs (cats Forman et al , 1957, Laursen, 1963, Stevens et al , 1961) Although it has been stressed that some responses may be elicited from adjacent structures (cats Akert et al , 1951), it has been shown that at least the contralateral turning movements of the head are characteristic for stimulation of the caudate nucleus (cats Laursen, 1963)

Apart from these studies, experimental studies dealing with the effects of lesions have revealed that unilateral destruction of this structure results in abnormal motor phenomena such as ipsilateral circling, contralateral extensor hypertonia, ipsilateral flexor hypertonia and disturbed postures in which the neck and the body are curved towards the side of the lesion (rabbits White et al , 1954, for review Martin, 1967) As Laursen (1963) already has summarized in his excellent review, a number of conflicting data resulting from bilateral lesions have been reported either no effects at all are induced, or effects such as propulsive hyperkinesias and disturbances of proprioceptivity are induced According to Laursen (1963), the "positive" effects are largely due to lesions involving other brain structures, recent findings, however, have indicated that lesions restricted to the caudate nucleus itself result in specific motor disturbances (cats Liles et al , 1969a)

Apparently, the experimental data are consistent with those derived from clinico-pathological studies, and indicate that the caudate nucleus is, in any case, involved in the control of movement and posture (Dieckmann et al , 1968, Jung et al , 1960)

For a long time, it was generally accepted that the caudate nucleus exerted an inhibitory influence on both the behavioural and neurophysiological level (Akert et al , 1951, Dusser de Barenne et al , 1942, Freeman et al , 1940, Gerebtzoff et al , 1941, Hess, 1944, Mettler et al , 1949, Rougeul, 1965) In the nineteen sixties, this concept has undergone a strong revision In view of the findings that low frequency stimulation (1-10/sec) of the caudate nucleus produced cessation of bar-pressing accompanied by the appearance of "caudate spindles" in the electrocorticogram on the one hand, and high frequency stimulation (30-300/sec) of this nucleus produced arousal accompanied by the appearance of a desynchronization of the electrocorticogram on the other hand, Buchwald and his co-workers have suggested that the caudate nucleus is involved in at least two separate, opposing, functional systems,

i e a low frequency inhibitory system and a high frequency facilitatory system (cats Buchwald et al , 1960, 1961a, b) Indeed, Liles et al (1969a, b) have demonstrated that there are two different functional systems within this nucleus in cats a system which inhibits cortically-induced movements, and a system which facilitates cortically-induced movements, the first system is restricted to the rostroventral part of the head of the caudate nucleus, whereas the second is restricted to the posterodorsal part of the head of the caudate nucleus These findings have supported the suggestion made by Mingazzini (1912) and Davison et al (1940) that there exists a functional organization within this nucleus in man Experimental studies in animals have confirmed that there is such a functional differentiation electrical stimulation of different points within the caudate nucleus results in different effects (cats Forman et al , 1957, cats O'Donohue et al, 1967, monkeys Rosvold et al , 1956, cats and monkeys Rozhanskii et al , 1957), and lesions of different parts of the caudate nucleus also result in different effects (monkeys Divac et al, 1967, cats and monkeys Divac, 1968, 1972, cats Liles et al , 1969a)

A further indication in favour of the highly complex nature of the caudate function on the behavioural level is the finding that electrical stimulation of the caudate nucleus inhibits motor responses elicited from ipsilateral, cortical structures, but facilitates motor responses elicited from contralateral, cortical structures (cats Krauthamer et al , 1967) Again, these data indicate that the caudate nucleus not only regulates motor activity by inhibitory processes, but also by facilitatory processes As long as half a century ago, the Vogt's (1920) already postulated that the caudate nucleus should be considered as a co-ordinating centre emitting both excitatory and inhibitory influences tremor and chorea were thought to be due to disruption of the inhibitory influence, and akinesia was thought to be due to disruption of the excitatory influence

Although electrophysiological data, derived from gross electrical recordings following electrical stimulation of the caudate nucleus, have been interpreted as indicating mainly an inhibitory function on the neurophysiological level (Demetrescu et al , 1962, 1965, Dusser de Barenne et al , 1942, Fox et al , 1962, Freeman et al , 1940, Gerebtzoff, 1941, Heuser et al , 1961, Mettler et al , 1949, Spehlmann et al , 1960), more sophisticated studies, using either extra-cellular or intracellular recordings following electrical stimulation of the caudate nucleus, have demonstrated that electrical stimulation of this nucleus induces highly complex synaptic activities in other brain nuclei, varying from single excitatory postsynaptic potentials (EPSP's) or inhibitory postsynaptic potentials (IPSP's) to integrated sequences of EPSP's and IPSP's (Connor, 1968, Frigyesi et al , 1967, 1970, 1971, Krauthamer et al , 1967, Malliani et al , 1967, Purpura et al , 1967) From these data, it appears extremely difficult to ascribe either an inhibitory or facilitatory function to the caudate nucleus Furthermore, it is still an open question of whether neurophysiological activities evoked from the caudate nucleus actually originate from intracaudate elements

or from fibres passing through this nucleus (Goldring et al., 1963, Marco et al., 1966) Moreover, it has been found that similar behavioural responses induced by different manipulation techniques are accompanied by quite different electrophysiological responses of intracaudate elements (Buchwald et al., 1969) In view of these considerations, it appears extremely difficult to correlate neurophysiological data with behavioural data

2 1 2 REGULATION OF COMPLEX BEHAVIOURAL ACTIVITIES

Caudate cells are normally hyperpolarized, and have a very low degree of spontaneous activity (Buchwald et al., 1969, Herz et al., 1968, Hull et al., 1969, Purpura et al., 1967) According to Hull et al (1969), it seems to be likely that the relatively small number of output cells, only firing when they simultaneously receive a number of different inputs, represent a high level of integration This suggestion is compatible with the observation that quite a number of various impulses evoked from peripheral and central sites converge on striatal cells (Albe-Fessard et al., 1960a, b), and that impulses evoked from the caudate nucleus modify the reception of afferent sensory information from auditory, visual and somesthetic receptors (Buchwald et al., 1962, Krauthamer et al., 1965, 1967, Amato et al., 1971, La Grutta et al., 1969a, b) These data are in agreement with the suggestion that the caudate nucleus may function "on a high level of integration" (Buchwald et al., 1961b, 1962, Laursen, 1963)
Indeed, behavioural studies have shown that the following, highly complex, behavioural performances are affected when this part of the brain is partially destroyed conditioned instrumental responses such as the acquisition of passive avoidance (cats Fox et al., 1964, rats Kirkby et al., 1968, rats Mitcham et al., 1972, rats Schmaltz et al., 1972, rats Winocur et al., 1969), delayed response (cats Divac et al., 1968, rats, cats and monkeys Divac, 1972, see also Potegal, 1972), absolute spatial discrimination (rats Potegal, 1969), spatial alternation (rats Chorover et al., 1963, rats Gross et al., 1965), delayed alternation (rats, cats and monkeys Divac, 1972, monkeys Rosvold et al., 1956), object reversal (monkeys Divac et al., 1967), bar-pressing extinction (monkeys Butters et al., 1968) and delayed successive visual discrim nation (monkeys Cohen, 1972) The fact that classical discrimination learning is not affected in neostriatal-damaged animals (rats Brown et al., 1938, rats Ghiselli et al., 1938, monkeys Rosvold et al., 1956, cats Thompson et al., 1961) indicates that the above-mentioned deficiencies are not due to a generalized deterioration in behaviour
Further indications in favour of the highly complex nature of caudate function are the recent observations that electrical stimulation of the neostriatum can retroactively impair one-trial inhibiting avoidance learning (rats Wyers et al., 1968, 1971, cats Wilburn et al., 1972), food-motivated complex maze learning

(rats: Peeke et al , 1971) and extinction of appetitively motivated responses (Herz et al., 1971).

In view of these data, it appears that the caudate nucleus not only functions as a part of a pure motor system regulating posture and simple movements, but also as a part of a system regulating highly complex behavioural activities; in chapter 6, the last-mentioned aspect will be discussed in more detail. In fact, the separate lines of evidence, together with the experimental results of the present investigations, will be put together into a single coherent interpretation.

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2 2. ANATOMICAL ASPECTS OF THE CAUDATE NUCLEUS IN CATS

The investigation of the anatomy of a specific brain structure is a prerequisite for functional studies, since it may give, at least, a limited interpretation of its physiological function (Brodal, 1969; Jung et al., 1960) On the other hand, the involvement of specific pathways is dependent on the concomitant activity of other parts of the nervous system· fibres may or may not conduct impulses. Thus, the number of fibres connecting one structure with another is less important in this respect.
The caudate nucleus, together with the putamen, is referred to as the neostriatum (Hunt, 1918). The neostriatum is phylogenetically younger than the paleostriatum, which involves both the globus pallidus externus and the globus pallidus internus, in cats, the structure homologous with the globus pallidus internus is the nucleus entopeduncularis. In the neuro-anatomical literature, the neostriatum and the paleostriatum are often defined as the basal ganglia; however, no generally accepted agreement with respect to the usage of this term exists (Mettler, 1968).

2 2 1 LOCALIZATION

The caudate nucleus is a telencephalic structure which borders on the wall of the anterior horn and the body of the lateral ventricle (figs 1 and 2). The rostral pear-shaped part lateral to the anterior horn is called the head (caput nuclei caudati (caput caudati)).
The anteroventral aspects of this caput are adjacent to the nucleus accumbens; the rostrodorsal parts are accompanied by the subcallosal fasciculus. The lateroventral aspects of the caput are adjacent to the putamen; these nuclei, however, are incompletely separated by fibres from the anterior limb of the internal capsule. The caput of the caudate nucleus continues dorsoposteriorly, being directed backwards on the dorsolateral side of the thalamic nuclei, and is called the body. The body describes a C-shaped course following the direction of the crus fornicis and fimbria, and is directed downwards into the inferior horn of the ventricle, this part is defined as the tail of the caudate nucleus The tail terminates near the corticomedial part of the amygdala In its course along the medial part and superior wall of the lateral ventricle, the tail is accompanied by the stria terminalis.

2 2 2 FIBRE CONNECTIONS

The anatomical connections of the basal ganglia, including those of the caudate nucleus, have recently been reviewed by several workers (Brodal,

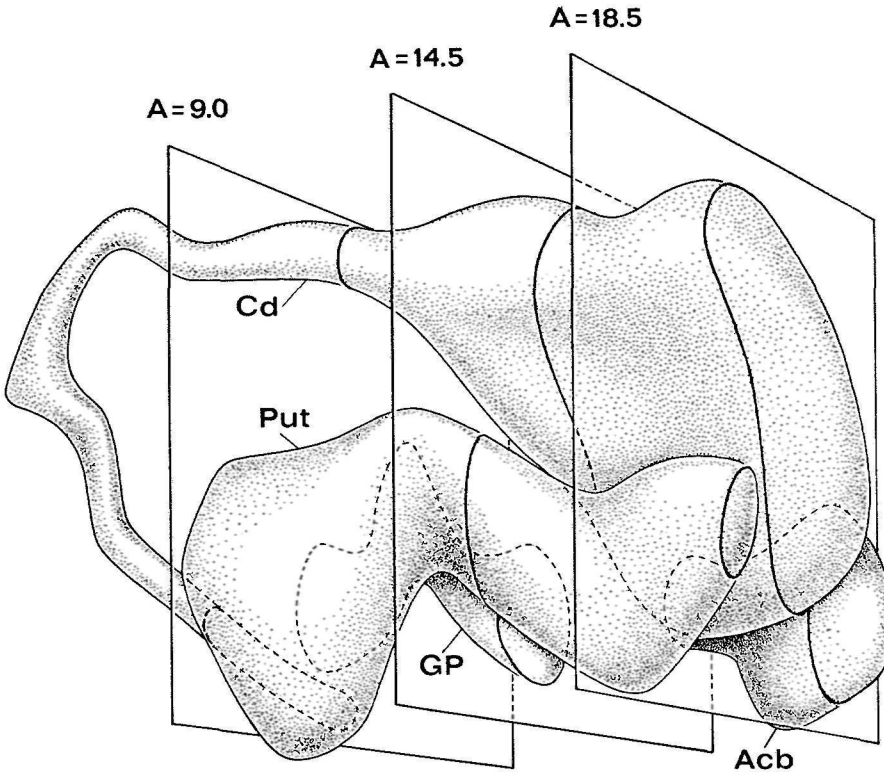

fig 1. A rostrolateral view of a three-dimensional reconstruction of the caudate nucleus (Cd), putamen (Put), globus pallidus (GP) and nucleus accumbens (Acb) in the cat. After a reconstruction by Lohman, A. H. M. Institute of Anatomy, University of Nijmegen, The Netherlands.

1969; Carpenter, 1961; Carpenter et al., 1967; Laursen, 1963; Mettler, 1968; Nauta et al., 1961; Nauta et al., 1966). For an extensive review including detailed references, the reader therefore is referred to these articles. There are many conflicting data with respect to the anatomy of the caudate nucleus. The controversy is due in part to the relatively inaccessible position of the caudate nucleus, to the complexity of the fibre bundles, and to the difficulty of placing discrete lesions. As the present knowledge is far from complete, the account given below presents only those connections in the cat brain for which conclusive evidence is available.

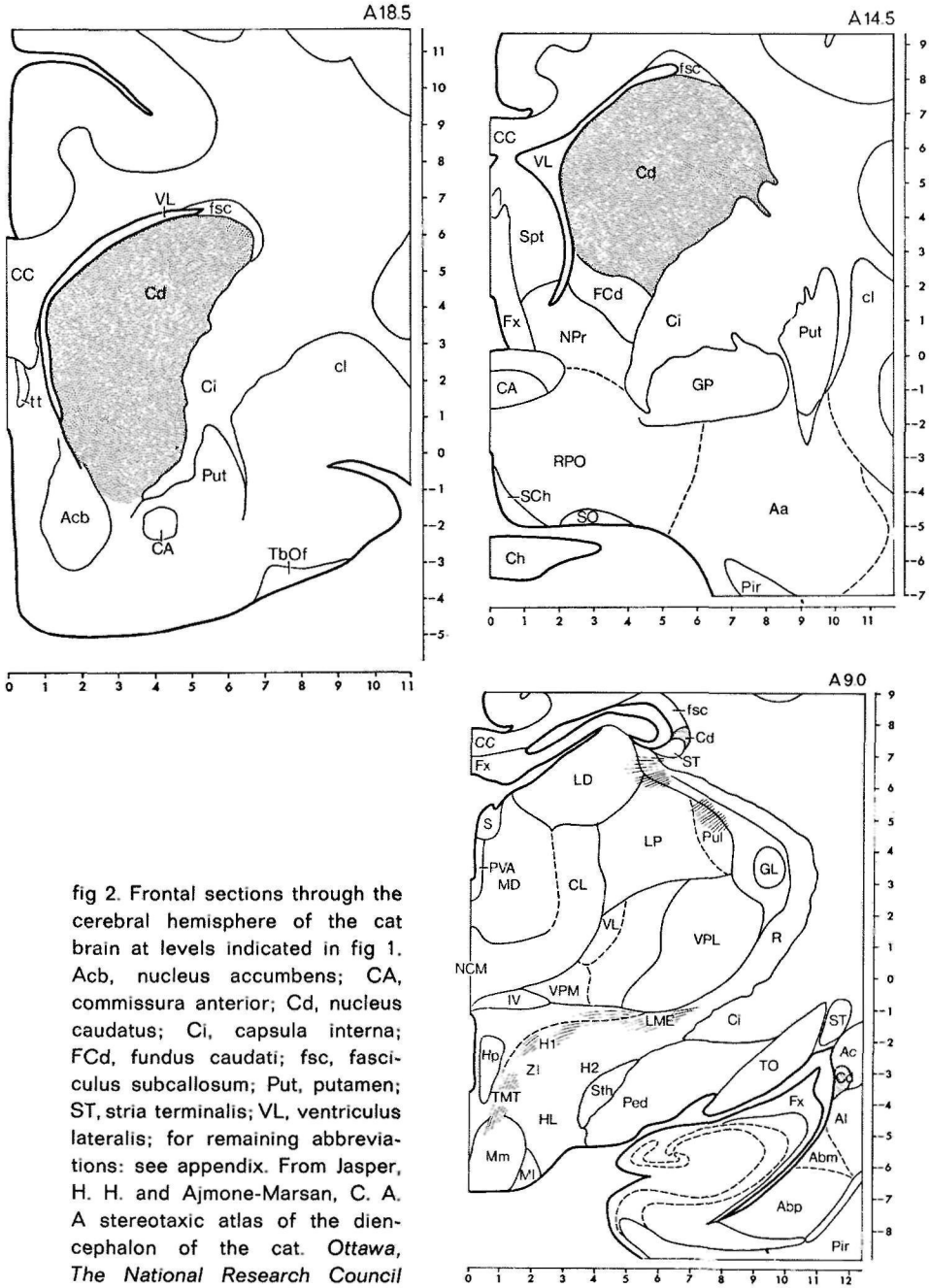

fig 2. Frontal sections through the cerebral hemisphere of the cat brain at levels indicated in fig 1. Acb, nucleus accumbens; CA, commissura anterior; Cd, nucleus caudatus; Ci, capsula interna; FCd, fundus caudati; fsc, fasciculus subcallosum; Put, putamen; ST, stria terminalis; VL, ventriculus lateralis; for remaining abbreviations: see appendix. From Jasper, H. H. and Ajmone-Marsan, C. A. A stereotaxic atlas of the diencephalon of the cat. *Ottawa, The National Research Council Canada (1954).*

2 2 2 1 Afferent fibres (fig 3)

The caudate nucleus receives axons from all parts of the neocortex in a topographical pattern, especially from the "suppressor" bands 2s, 3s, 8s and 19s, and from the areas 4, 6, 8 and 19 (Webster, 1965) A number of electrophysiological experiments, including both extracellular and intracellular studies, have yielded physiological evidence compatible with these projections (Buchwald et al , 1969, Hull et al , 1969, Rocha-Miranda, 1965) An example of the well-organized projection is the massive projection from the ventral half of the posterior sylvian and ectosylvian gyri, which terminates upon the dendritic spines of the ventromedial aspects of the caput caudati (Siegel et al , 1971) Electrophysiological evidence bearing upon these temporo-caudate connections is lacking, apart from one study in which local application of KCl on the primary auditory cortex reduced the caudate potentials evoked by acoustic stimulation (La Grutta et al , 1966). Furthermore, an extremely small amount of crossed cortico-caudate connections have been found (Webster, 1965). Such projections have also been described on the basis of strychnine neuronography (Sachs et al , 1949) Apart from the cortical connections, the caudate nucleus receives fibres from the substantia nigra (divisio compacta), the ventral tegmental area (Moore et al , 1971) and from some thalamic nuclei such as the nucleus parafascicularis thalami, the nucleus centrum medianum thalami, the nucleus centrolateralis thalami, the nucleus paracentralis thalami and the nucleus centromedialis thalami (Mehler, 1966, Nauta et al , 1954), however, most of the thalamic fibres primarily terminate in the putamen, some terminate in the nucleus accumbens and only very few terminate in the caudate nucleus The nigro-caudate projections have been previously described in the rat on the basis of the Falck-Hillarp fluorescence histochemical method (Anden et al , 1964, Dahlstrom et al , 1965), while recent electrophysiological and biochemical studies have yielded additional data for the cat (Albe-Fessard et al , 1967, Bédard et al , 1969, Connor, 1968, Faull et al , 1969, Feltz et al , 1969, Frigyesi et al , 1967, Hull et al., 1970, Moore et al , 1971, Poirier et al , 1969) Frigyesi et al (1970, 1971) have presented electrophysiological evidence in favour of the thalamo-caudate connections Brodal et al (1960) have found that neurons of the linear nucleus of the raphe have terminals ending in the caudate nucleus, histochemical investigations by Parent et al (1969) and Poirier et al (1969) are in agreement with these findings Finally, axon impregnation studies utilizing the Fink-Heimer method have shown that small caliber axons enter the caudate nucleus from the brain stem (Nauta et al , 1969).

2 2.2.2. Efferent fibres (fig 3)

The caudate nucleus sends fibres mainly to the globus pallidus and the nucleus entopeduncularis (Johnson et al., 1959; Nauta et al., 1961, Voneida, 1960). Apart from the massive projections to the pallidal nuclei, the caudate nucleus sends fibres to the substantia nigra (Johnson, 1961; Nauta et al., 1961; Voneida, 1960). It is apparent from the above that there exists a reciprocal relationship between the substantia nigra and the caudate nucleus. Although most authors report that the caudate nucleus sends fibres particularly to the so-called divisio reticularis, a recent study has shown that both the divisio reticularis and the divisio compacta receive caudate fibres (Grofova et al., 1970; Rinvik et al., 1970).
According to Mettler (1968), many conflicting results with respect to caudato-cortical and caudato-thalamic efferents are reported, no conclusive evidence in favour of their existence has been presented.
As the main efferent outflow of the caudate nucleus goes to the pallidal nuclei, the termination of this transneuronal outflow is of great interest (fig 3). In general, the efferent fibres of the paleostriatum are rather complex and are not known in all details Most authors describe three major bundles: the ansa lenticularis, the fasciculus lenticularis and the subthalamic fasciculus These bundles inter alia contain fibres terminating in the thalamic nuclei (the nucleus centrum medianum thalami, the nucleus ventralis lateralis and anterior thalami), the nucleus subthalamicus, the zona incerta and the substantia nigra, divisio reticularis (for review: Mettler, 1968).

A. From the neuro-anatomical point of view, it should be mentioned that the major part of the pallidal outflow is directed to the thalamic nuclei, while the efferent fibres running to the mesencephalic reticular formation, the so-called intercalated station to the spinal cord, are relatively scanty. In spite of the relatively small caudato-pallido-spinal connections these transneuronal efferents have received much attention in clinical neurology. the concept of the extrapyramidal motor system and of the extrapyramidal motor diseases was, in part, based upon these tracts (Wilson, 1914). In the light of the facts mentioned below, this concept has undergone a strong revision and is, in fact, meaningless according to present day knowledge (for review. Brodal, 1969). The mentioned thalamic nuclei, upon which the pallidal nuclei project, send fibres primarily to the neocortex, which, in turn, sends fibres to the caudate nucleus (fig 4). Apparently, a closed circuit between the caudate nucleus and the neocortex appears to exist the so-called cortico-caudato-pallido-thalamo-cortical circuit (fig 5). Electrophysiological data are now being gathered on this circuitous route (for review. Frigyesi et al., 1970, 1971). The cortical areas which are important links in the mentioned caudato-cortical loop, are also the origin of the so-called pyramidal tracts (Kuypers, 1960; Lawrence et al , 1968)
Thus, the caudate nucleus indirectly influences the spinal cord through the

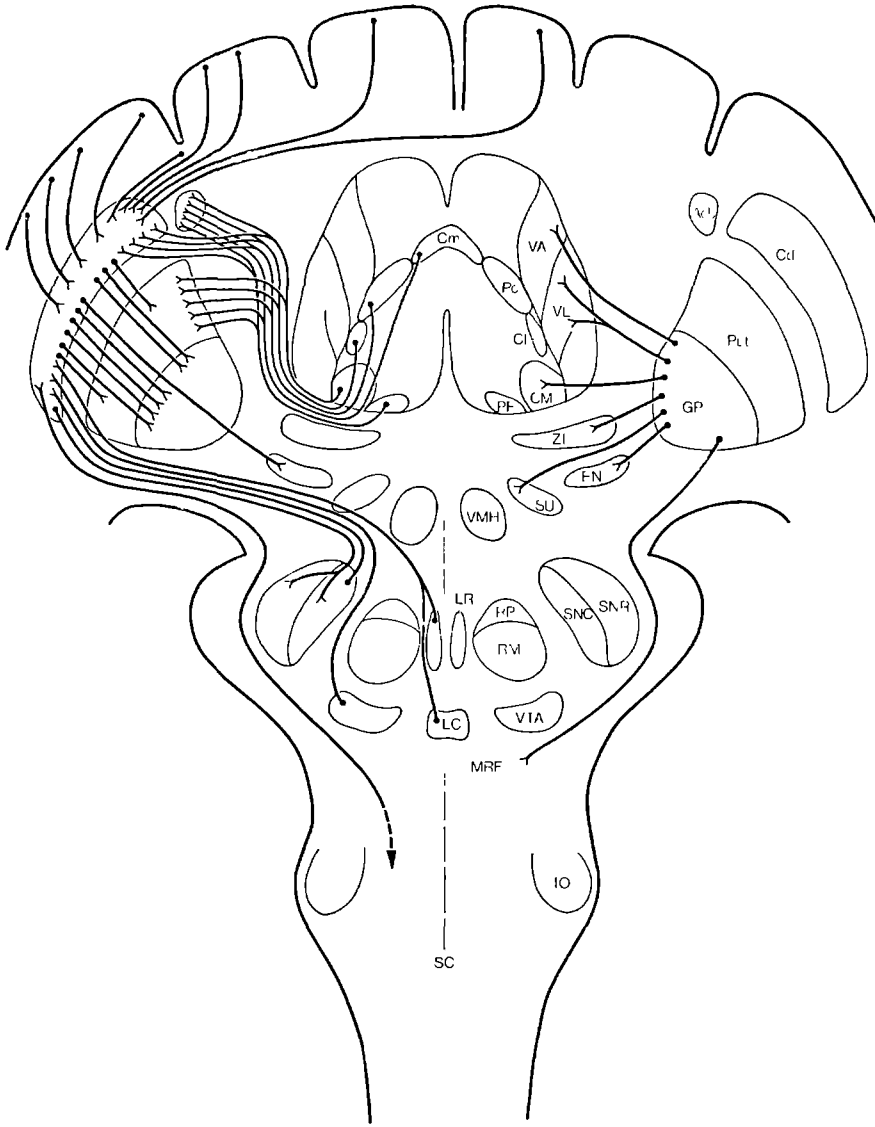

fig 3 Schematic diagram of afferent and efferent connections of the caudate nucleus (left side) and major outflow of the globus pallidus (right side) in the cat For abbreviations see appendix Modified from Brodal, A Neurological anatomy in relation to clinical medicine *London, Oxford University Press (1969)*

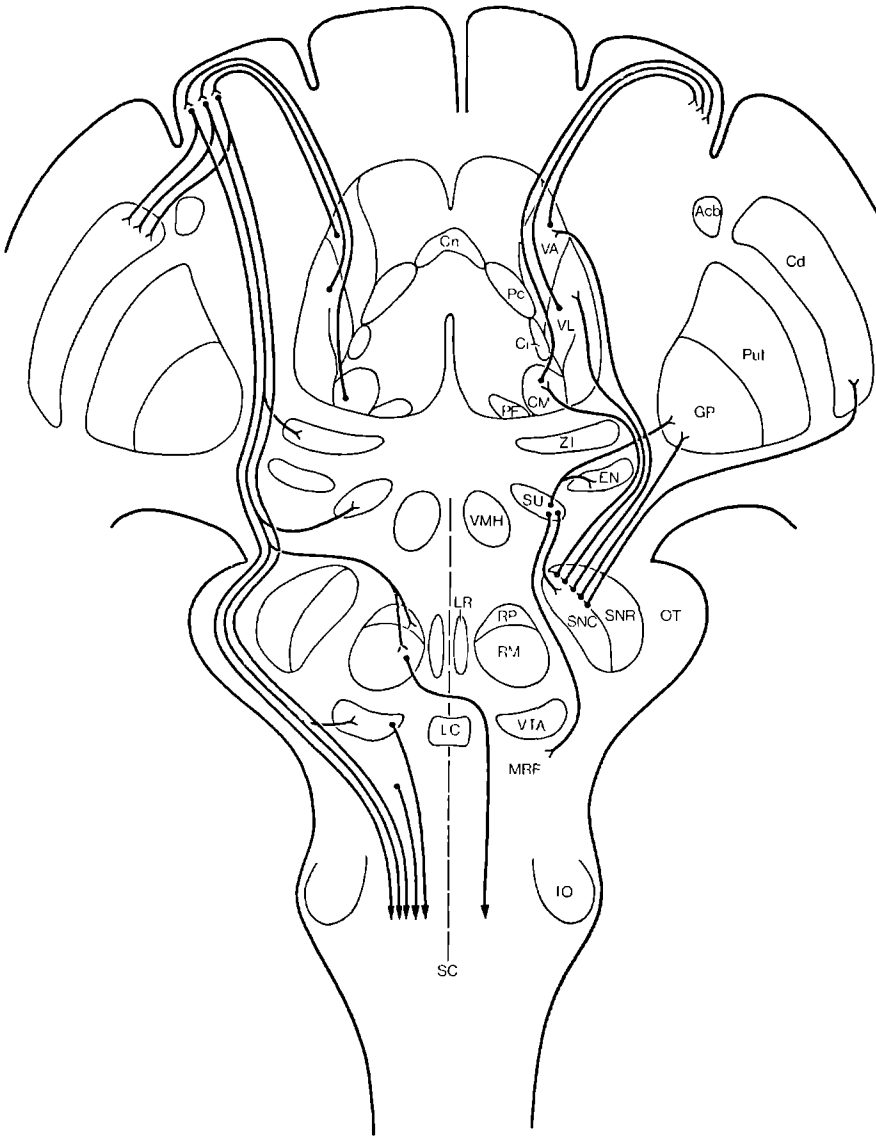

fig 4. Schematic diagram of the afferent connections of nuclei to which the major outflow of the globus pallidus in the cat is directed For abbreviations see appendix. Modified from the same source as in fig 3

pyramidal tracts Strictly speaking the concept of extrapyramidal motor system as referring to structures other than pyramidal is accordingly misleading and, thus, has lost its rational basis

B The second neuronal outflow from the pallidal nuclei runs to the nucleus subthalamicus which inter alia sends fibres to the globus pallidus and the substantia nigra, divisio compacta (fig 3), it is apparent from these pathways that there are more circuitous routes by which the caudate nucleus is connected with corticopetal fibres (fig 5) Only a small number of the subthalamic outflows is directed to the mesencephalic reticular formation, which transmits impulses to the spinal cord (fig 4)

C The third neuronal outflow from the pallidal nuclei runs to the substantia nigra (fig 3), the output from th s nucleus is inter alia directed to the globus pallidus and the nucleus ventralis lateral s and anterior thalami (fig 4)

Apart from the mentioned electrophysiological evidence compatible with the neuro-anatomical data, electrophysiological studies have presented data in favour of additional transneuronal connections of the caudate nucleus for instance, with the hippocampus (Costin et al , 1963), the dentate nucleus (Frigyesi et al , 1971, Ratecheson et al , 1969), the lobulus simplex and paramedian lobulus of the cerebellum (Fox et al , 1970) and the nucleus ventromedialis hypothalami (Dafny et al , 1967) It is apparent from the neuro-anatomical data that there is a large number of efferent caudate fibres, which transneuronally projects through the thalamic nuclei to the neocortex, and that there is a relatively small number of efferent caudate fibres, which transneuronally projects through structures of the mesencephalon to the spinal cord

In conclusion, the caudate nucleus not only receives fibres from both ascending and descending systems, but also sends projections to both systems Accordingly, it appears impossible to consider the neuro-anatomical data in this case as data which may restrict possible functions of this intercalated station On the other hand, it may be safely concluded that the caudate nucleus must be involved in integrative processes on a relatively high level because of its complicated relationship with other cerebral nuclei (fig 5)

2 2 3 INTRACAUDATE STRUCTURE

In general, our knowledge of the infrastructure of the caudate nucleus is relatively scanty Apart from a number of light microscope studies in different species (Bielschowsky, 1919, Glees, 1944, Ramon Y Cajal, 1911, Verhaart, 1950, Wilson, 1914), only a small number of electron microscope studies have been performed (Adinolfi et al , 1968, Fox et al , 1971, Kemp, 1968a, b, 1970a, b) In the caudate nucleus, at least four kinds of neurons are present

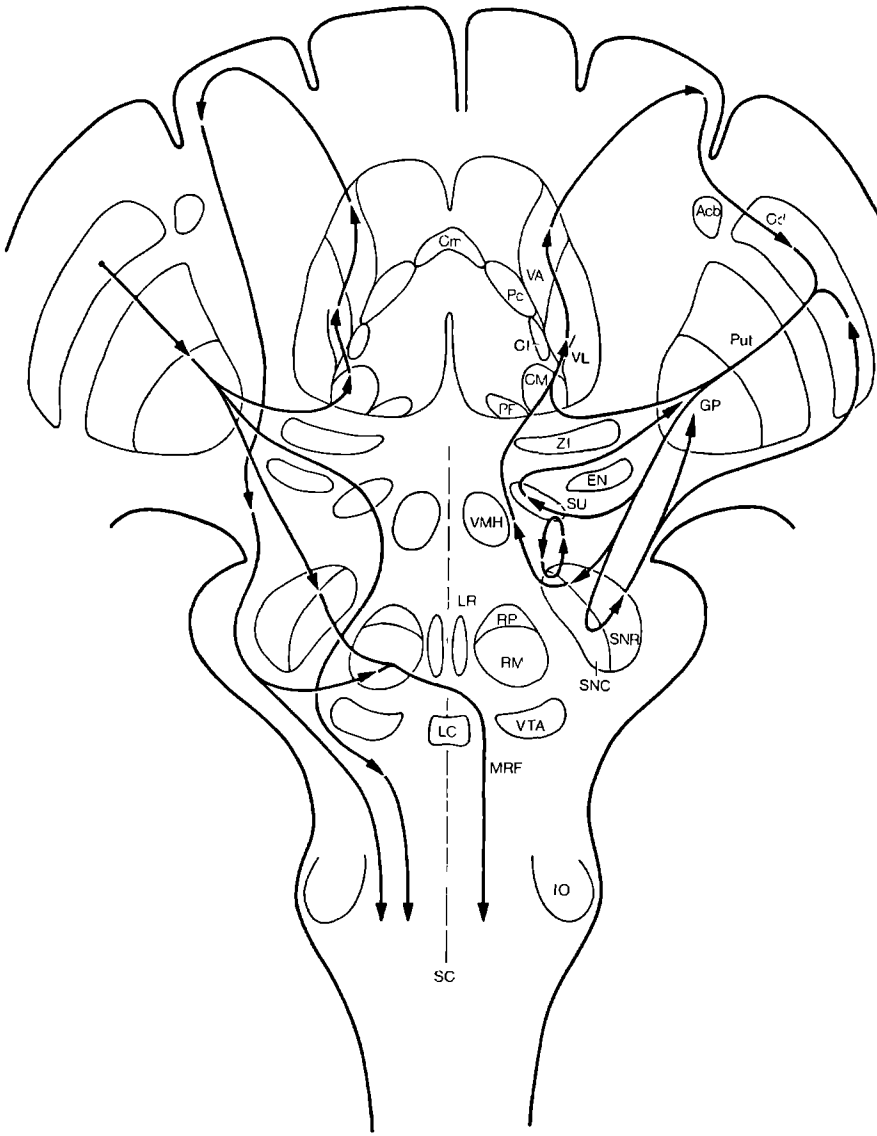

fig. 5 Schematic diagram of possible transmission of caudate impulses. For abbreviations, see appendix. Modified from the same source as in fig 3

(a) and (b) medium-sized cells with a diameter of about 10-18 μ either having spineless dendrites and rather long axons, or having dendrites covered with spines and rather short axons, (c) large-sized cells with a diameter of about 22 μ having rather long dendrites with or without spines and intermediate axons; and (d) small-sized cells with a diameter of about 7 μ having short, spineless dendrites and short axons (fig 6). These neurons, together with myelinated and non-myelinated fibres, neuroglial cells and small blood vessels form a dense neuropile marked by the typical structures of dendritic spines (fig 6). According to Kemp (1968b), the majority of the non-myelinated fibres is intrinsic, as a large number remain after combined cortical and thalamic lesions; however, these data need additional evidence from experiments in which the effects of nigral lesions are studied, since electrophysiological studies have indicated that extremely small fibres are involved in the nigro-caudate connections (Frigyesi, 1967).

Apart from relatively few granular axon terminals containing large dense cores, two different kinds of agranular axon terminals have been found (a) axospinous, axodendritic, or axosomatic contacts containing densely packed, small vesicles with a diameter of 400-500 Å, and (b) axodendritic or axosomatic contacts containing mainly flattened vesicles In view of the fact that many caudate efferents have short collaterals, it is extremely difficult to investigate whether synapses belong to these collaterals, or to intrinsic fibres.

In studies concerning the functional significance of different synaptic contacts, Eccles (1964) has suggested that axodendritic spine synapses are predominantly excitatory in function, and that axosomatic synapses may be chiefly inhibitory Accordingly, Adinolfi et al. (1968) have suggested that the excitatory postsynaptic potentials reflect a functional organization involving predominantly axodendritic spine synapses. It is of interest to note that synaptic endings containing elongated and egg-shaped vesicles and terminating on the initial segments of caudate spiny neuron axons, have morphological features similar to those which are inhibitory in nature (Eccles, 1967; Fox et al , 1970). However, conclusive evidence with respect to the physiological function of synapses is not available The same holds true for the relationship between different synapses and different neurotransmitters

In summary, the caudate nucleus is a complex structure characterized by dendritic spines and a high number of non-myelinated fibres of which the origin, course and destination are far from clear, our knowledge with respect to their intrinsic synaptic organization is scanty, and remains to be elucidated.

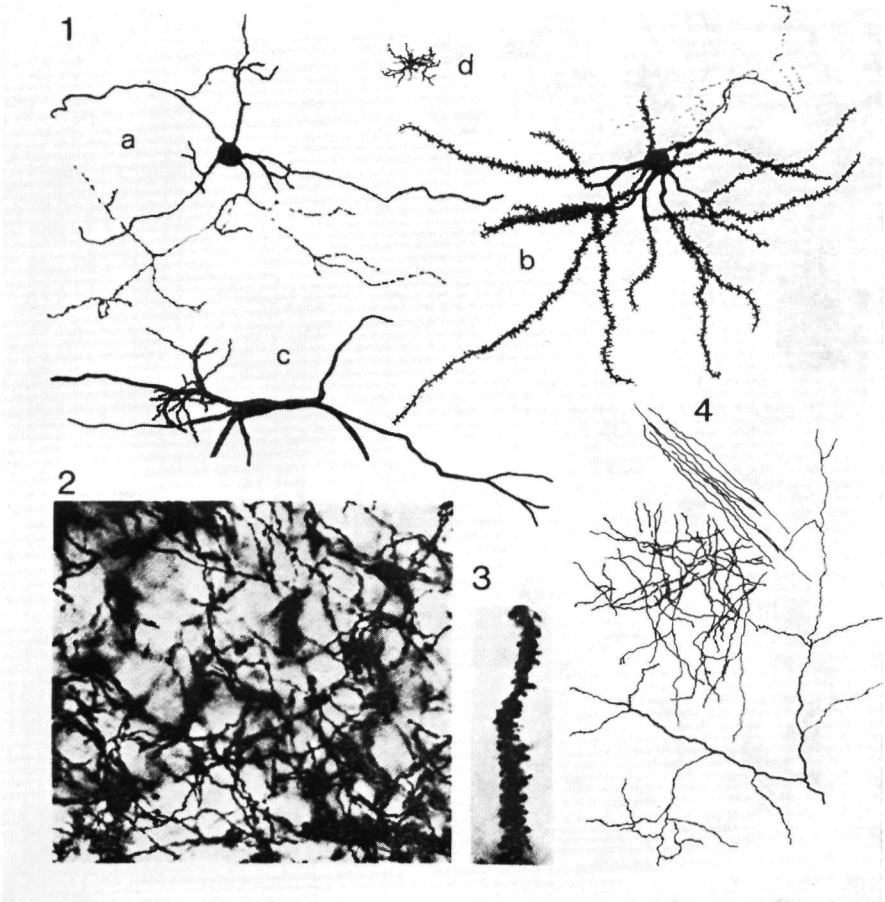

fig 6. (1) camera lucida drawings of the four cell types in the caudate nucleus of cats: a and b, medium cells with and without spines; c, large cell; d, small cell. (2) photograph of the axonal plexus of normal caudate nucleus. X 576. (3) photograph of the dendrite of a medium sized cell. X 540. (4) camera lucida drawings of the axonal plexus. From Kemp, J. M. *Brain Res. 11, 468 (1968).* Reprinted by permission of the publisher.

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2 3 RELEVANT NEUROTRANSMISSION PROCESSES IN THE CAUDATE NUCLEUS OF CATS

Transmission of impulses between nerve fibres within a specific brain structure is an essential prerequisite for the transmission of information within that structure, i e its physiological function The complex structural and functional unit involved in this transmission process is the synapse It is well known that there exists a mechanism by which arrival of an impulse enables the nerve ending to release chemical mediators (neurotransmitters) from the presynaptic membrane The action of neurotransmitters with sensitive, postsynaptic sites called receptors may produce either a depolarization or a hyperpolarization of the postsynaptic membrane

It is not useful to extensively review the vast literature which has accumulated to support the hypothesis of neurochemical transmission, there are several excellent monographs available (Eccles, 1964, Hornykiewicz, 1966, McLennan, 1963, Phillis, 1970) It is useful, however, to recall the criteria developed for the identification of neurotransmitters in peripheral systems (Hebb, 1970, McLennan, 1963, Werman, 1966) Firstly, the substance must be found in those neurons from which it is released, this criterion involves its synthesis and storage within the nerve ending and its release following stimulation of the presynaptic nerve ending Secondly, the substance must induce a postsynaptic action which is terminated within a restricted time, this criterion involves either inactivating enzymes present at, or adjacent to, the site of its action, or re-uptake of the substance in the presynaptic nerve ending Thirdly, the postsynaptic action of the substance must mimic the action of stimulation of those cell bodies or axons, which are loaded with this substance or with the enzymes required for its synthesis Finally, pharmacological agents which modify the operation of the substance must similarly affect the action of the applied substance

Current reports have revealed that several compounds such as acetylcholine, dopamine, noradrenaline, serotonin and possibly also gamma-amino-butyric acid, histamine, glutamine, glycine and purines may meet most of these requirements (Bradley, 1968, Burnstock, 1972, Hebb, 1972, Hornykiewicz, 1966, Salmoiraghi, 1966) Accordingly it is of relevance to investigate whether these compounds occur within the caudate nucleus, and whether these compounds may function as neurotransmitters

The caudate nucleus contains inter alia acetylcholine (Fahn et al , 1968), dopamine (Bertler, 1961), serotonin (Paasonen et al , 1956), gamma-amino-butyric acid (Baxter et al , 1960) and histamine (Adam et al , 1960) As the main interest in the present study is directed towards dopamine, serotonin and, to a lesser extent, acetylcholine, the account given below is restricted to these compounds

In comparison with other brain areas, the caudate nucleus contains the largest amount of dopamine in mammals (Bertler et al., 1959; Bertler, 1961; Carlsson, 1959; Ehringer et al., 1960; Gutman et al., 1967; Laverty et al., 1965; Sano et al., 1959). With regard to its localization in rats, it is now generally accepted that it is restricted to very fine fibres, running from the substantia nigra to the neostriatum, and to the varicosities in these nerve endings (Andén et al , 1964a, 1965, 1966a,b,c; Dahlstrom et al., 1964, Fuxe et al., 1964, 1965, Hokfelt et al., 1969). Although the distribution of dopamine in cats has not been studied by means of histochemical fluorescence methods, much biochemical and neuropharmacological data have indicated that a similar distribution occurs in the brain of cats (Bédard et al., 1969, McLennan, 1964; Moore et al , 1969; Parent et al., 1969; Poirier et al., 1965, 1967, 1969a; Riddell et al., 1971; Sourkes, 1966). Furthermore, all of the enzymes responsible for both dopamine synthesis from L-tyrosine and its transformation to homovanillic acid are also found within this nucleus (Andén et al., 1966a, Axelrod et al., 1959, Bogdansky et al., 1957; Carlsson, 1959, Javoy et al , 1972; Masuoka et al., 1963, McGeer et al , 1965; Udenfriend et al., 1959). The major metabolic pathways are summarized in fig 7; for an extensive review, the reader is referred to Carlsson (1959), Hornykiewicz (1966), Milhaud et al. (1962), Rutledge et al. (1967) and Seiler et al. (1971). As the activity of the enzyme dopamine-β-hydroxylase is very low (Coyle et al , 1971; Reis, 1971), noradrenaline is almost absent from this nucleus (Vogt, 1954).

The following facts suggest that dopamine may be considered as a putative neurotransmitter within the caudate nucleus

First, dopamine is released from the nigro-caudate neurons in which it is synthesized (Besson et al , 1969a,b, 1971; Riddell et al , 1971; Javoy et al , 1970).

Second, dopamine is stored within vesicles in the presynaptic nerve (Hokfelt *et al.*, 1969).

Third, dopamine is released either during rest (McLennan, 1964) or during electrical stimulation of the presynaptic nerve (Portig et al., 1969, Riddell et al., 1971)

Fourth, dopamine is rapidly metabolized following its release (McKenzie et al., 1968; Portig et al , 1968; Riddell et al., 1971) Moreover, its action is terminated by re-uptake in the presynaptic nerve in which it is either stored in vesicles or metabolized. Although such a re-uptake mechanism in in vivo experiments has not yet been shown, in vitro experiments using synaptosomes suggest that processes similar to those occurring in peripheral synapses are involved (Iversen, 1971).

Fifth, dopamine induces a characteristic action: elicitation of excitatory postsynaptic potentials (EPSP's) in a small number of caudate cells and elicitation of inhibitory postsynaptic potentials (IPSP's) in the majority of caudate cells

(Bloom et al , 1965, Herz et al , 1966, 1968, McLennan et al , 1967, York, 1967), in view of these findings, it has been postulated that dopamine is a post-synaptic inhibitory agent

Sixth and last, caudate cells which are inhibited by stimulation of the substantia nigra are inhibited by the application of dopamine (Connor, 1970, Feltz, 1970a,b) In contrast, caudate cells which are excited by stimulation of the substantia nigra are quite insensitive to the application of dopamine (Feltz, 1972a,b) In this context, it is of importance to note that putamen cells which are excited by stimulation of the substantia nigra are also quite insensitive to the application of dopamine when low doses are used, but are excited when higher doses are used (York, 1970, 1972), York therefore suggests that there exist at least two types of dopamine-sensitive sites an inhibition-inducing type and an excitation-inducing type It is evident that one needs additional experiments in order to decide whether the above-mentioned data concerning the mimicing action of dopamine are valid or not

Apart from the last-mentioned fact, the remaining facts suggest that caudate dopamine fulfils a neurotransmitter role in this nucleus

2 3 2 ACETYLCHOLINE

Apart from dopamine, the caudate nucleus contains a very high amount of acetylcholine and all of the enzymes involved in its synthesis and degradation (Fahn et al , 1968, Feldberg et al , 1948, 1951, Fonnum, 1966, Gerebtzoff, 1959, Hebb et al , 1956, 1957, 1972, Koelle, 1954, McIntosch, 1941) With regard to its localization, it appears that at least the caudato-pallidal, caudato-nigral and caudato-cortical efferents are loaded with acetylcholine (Olivier et al , 1970) According to McLennan (1964), a small fibre bundle connecting some thalamic nuclei with the caudate nucleus may also contain acetylcholine, since electrical stimulation of these nuclei results in a release of acetylcholine within the caudate nucleus, these data are in agreement with those reported by Shute et al (1967) However, de-afferentation of the caudate nucleus does not lead to a change in acetylcholine, or in the activity of acetylcholinesterase and choline-acetylase within the caudate nucleus (Lynch et al , 1972, McGeer et al , 1971), they therefore suggest that intrinsic rather than extrinsic fibres contain acetylcholine

The neurotransmitter role of acetylcholine within the central nervous system is firmly established (Hebb, 1972) The following data may strengthen its role in the caudate nucleus of cats Acetylcholine is released during electrical stimulation of the caudate nucleus (McLennan, 1964), and it has a specific postsynaptic action elicitation of IPSP's in the central part of the head of the caudate nucleus, and elicitation of EPSP's in the area surrounding this part of the caudate nucleus (Bloom et al , 1965, McLennan et al , 1966)

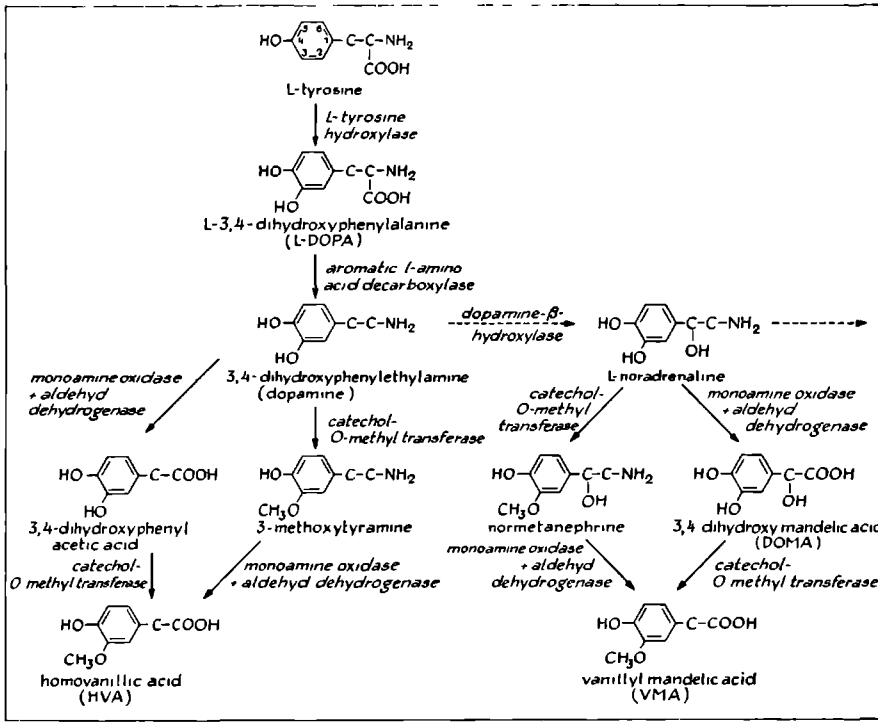

fig 7 The major metabolic pathways of dopamine in the caudate nucleus

Apparently, intracaudate acetylcholine has properties corresponding with those of acetylcholine occurring elsewhere in the brain.

2 3 3 SEROTONIN

A number of fluorescence studies in rats have shown that some vesicles in the neostriatal nerve endings contain serotonin (Andén et al., 1964b, Dahlstrom et al., 1964; Fuxe et al., 1968, Hokfelt et al., 1969); indeed, biochemical data indicate that the caudate nucleus contains serotonin (Bertler, 1961; Bernheimer et al., 1961, Paasonen et al., 1956, 1957; Sattin, 1966; Schubert et al., 1972). All of the enzymes responsible for the metabolism of serotonin are also present within the serotonin-containing nerves (fig 8; for review: Swonger, 1971). According to Parent et al. (1969) and Poirier et al. (1967, 1969b), these terminals in the cat belong to axons emanating from the nucleus raphe linearis,

nucleus paranigralis and other minor cell groups located in the ventromedial tegmental area below the third root fibres, since lesions in these areas reduce the serotonin content of the caudate nucleus (cf. rats: Giacolone et al., 1969; Heller, 1972; Kuhar et al., 1971; Ljunggren, 1971). However, it remains to be shown whether this change is due to the lesion of a monosynaptic pathway; the same holds true for the studies in which it has been shown that electrical stimulation of the mentioned nuclei induces a release of serotonin in the neostriatum of rats and cats (Aghajanian et al., 1967; Ashkenazi et al., 1972; Gumulka et al., 1969; Holman et al., 1972; Kostowski et al., 1969).
Recent work has supplied some evidence for the probable role of serotonin as a neurotransmitter in the central nervous system (Bradley, 1968): as has been mentioned, it is synthesized and stored within those nerves from which it is released (Graham-Smith, 1971; Hokfelt et al., 1969; Michaelson et al., 1962, Schubert et al., 1972; Takatsuka et al., 1970); its action is terminated within a restricted time (Aghajanian et al., 1967; Kostowski et al , 1969); and, finally, it has a characteristic postsynaptic action, which is mimiced by stimulation of the presynaptic nerve (Aghajanian, 1972; Bloom et al., 1972; Boakes et al , 1970; Curtis et al , 1969); such studies dealing with caudate serotonin in cats, however, are not yet available.

In summary, there is strong evidence that dopamine, acetylcholine and serotonin are essential regulators of the transmission of impulses within the caudate nucleus Given the importance of these compounds in the neurotransmission processes of the caudate nucleus, it is axiomatic that these processes will be contingent upon the function of this nucleus.

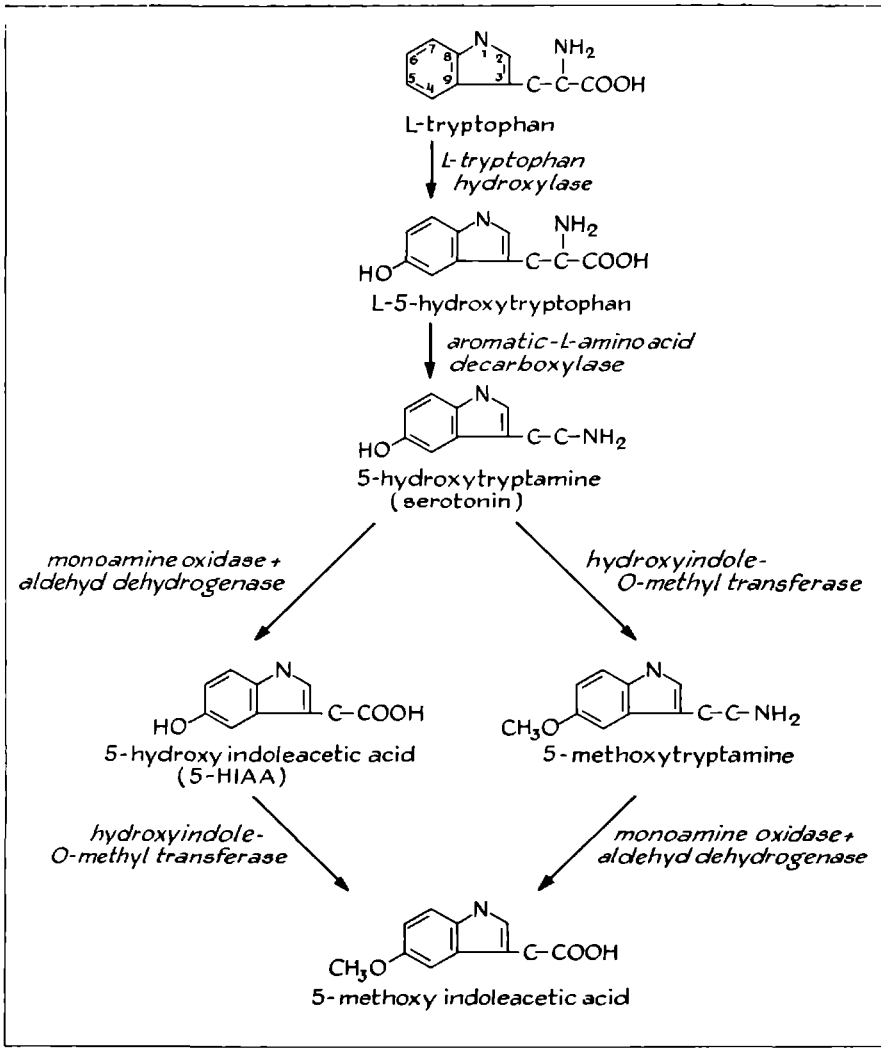

fig 8. The major metabolic pathways of serotonin.

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2 4 FUNCTIONAL ASPECTS OF NEOSTRIATAL DOPAMINE AND SEROTONIN

2 4 1 DOPAMINE

At the present time, the greatest part of the extensive literature on neostriatal dopamine refers to its role in behaviour elicited by substances which are supposed to interfere with the central dopamine mechanisms As a matter of fact, this research strategy has been mainly employed for studying the relationship between pharmacological mechanisms of psychoactive agents in the brain and their effects on behaviour However, these studies have indicated an unmistakable correlation between the behavioural set of the animal and central neurotransmission processes Therefore, the relevance of these "models" will be discussed first and, then, more basic studies will be considered

2 4 1 1 The apomorphine model

In 1874 (Harnack, 1874) it was reported that apomorphine systemically injected in rodents induced a compulsive sniffing, licking and biting stereotypy A number of experiments have confirmed these findings (Amsler, 1923, Costall et al , 1972b, Lal et al , 1972, McKenzie, 1972, Menge et al , 1967, Scheel-Kruger, 1970, Ther et al , 1962) It has been established that apomorphine mainly interferes with the turnover of brain dopamine it decreases the neostriatal amount of homovanillic acid (Goldstein et al , 1970, Roos, 1969), it induces a retardation of dopamine depletion following the administration of α-methyl-para-tyrosine (Anden et al , 1967b), it increases the fluorescence intensity in dopamine-rich terminals of the neostriatum (Anden et al , 1967b), and, finally, it inhibits the catechol-O-methyl-transferase (Belen'kii et al , 1966) Several studies have indeed indicated that the apomorphine-induced syndrome is inter alia mediated through the interaction of apomorphine with dopamine compounds which block dopamine activity inhibit the induced syndrome (Anden et al , 1967a, Costall et al , 1972b, Ernst, 1969, McKenzie, 1972)

Since local application of apomorphine into the dopamine-richest area of the brain, the neostriatum, also elicits the so-called apomorphine syndrome (Ernst et al , 1966, Fog et al , 1969), it has been postulated that apomorphine mainly interferes with neostriatal dopamine-sensitive sites (Anden et al , 1967b, Ernst, 1967, Roos, 1969) This is supported by the fact that neither inhibition of dopamine synthesis nor depletion of dopamine, depresses the apomorphine-induced effects (Ernst, 1967, Janssen et al , 1965, Lal et al , 1972, Rotrosen et al , 1972, Ther et al , 1962) Only one report mentions that reserpine inhibits the apomorphine-induced effects in mice (Fekete et al , 1970)

Despite this last finding, it seems likely that activation of the neostriatal dopamine mechanism is involved in the elicitation of the apomorphine-induced effects However, it is of relevance to consider the following data although some observers (Ungerstedt, 1971a) have reported that bilateral lesions in the nigro-neostriatal system abolish the effect of systemically injected apomorphine, other observers (Costall et al , 1972b) have reported that this is not the case, moreover, lesions in the tuberculum olfactorium are more effective in suppressing the apomorphine-induced syndrome than lesions in the neostriatum (McKenzie, 1972) In view of these findings, it will be clear that no clear-cut conclusive evidence in favour of the exclusive role of *neostriatal* dopamine in this syndrome has been presented

2 4 1 2 The dexamphetamine model

In various experiments with pigeons, mice, rats, guinea pigs, rabbits, cats, dogs, monkeys, apes and man, characteristic disorders of the patterning of complex movements are observed after large doses of dexamphetamine (Randrup et al , 1967, 1970) hyperactivity, stereotyped sniffing, licking and biting in rats, constant purposeless searching head movements in cats, compulsive pecking in pigeons, rapid sidewards movements of the body and forelimbs in squirrel monkeys, stereotyped movements such as sorting objects, manipulating things, polishing fingernails in man, etc For an extensive review of the so-called stereotyped movements, the reader is referred to Randrup et al (1970)

In a series of reports, it has been demonstrated that dexamphetamine interferes with brain monoamines it causes a release of brain noradrenaline, dopamine and serotonin into the extracellular space (Carlsson et al , 1965, 1966, Fuxe et al , 1970a, Glowinski et al , 1966a, b) ,it inhibits the intracellular monoamine oxidases which are responsible for the conversion of dopamine, noradrenaline and serotonin into their corresponding deaminated products (Glowinski et al , 1966a), and, finally, it probably has direct dopamine-receptor activating properties (Feltz et al , 1972, van Rossum et al , 1964, Smith, 1963), although this action is still under discussion (Graham et al , 1971, Hanson, 1967, Rech et al , 1970, Scheel-Kruger, 1971)

A large number of pharmacological experiments have demonstrated that the dexamphetamine-induced stereotypies are largely based upon the activation of the dopamine mechanisms within the brain (Munkvad et al , 1968, Randrup et al , 1966a, b, van Rossum, 1970, Scheel-Kruger et al , 1967a, b, Taylor et al , 1971) if the synthesis of dopamine and noradrenaline is inhibited by α-methyl-para-tyrosine, the dexamphetamine-induced stereotypies are inhibited, but can be restored by L-DOPA, the precursor of dopamine and noradrenaline, if the synthesis of noradrenaline alone is inhibited, the dexamphetamine-induced stereotypies are unaffected

In view of the following findings, it seems reasonable to assume that the dexamphetamine-induced stereotypies are mediated by the activation of the dopamine mechanisms within the neostriatum (a) if rats pretreated with α-methyl-para-tyrosine, nialamide and dexamphetamine respectively receive bilateral injections of dopamine (200 ug/1 ul) into the neostriatum, a rapid restoration of the dexamphetamine stereotypy is produced (Fog et al , 1966, 1967), (b) when the neostriatum is bilaterally lesioned in rats, systemic injections of dexamphetamine remain ineffective (Fog et al , 1970, Naylor et al , 1972), and (c) when rats, neostriatally injected with compounds which decrease the dopamine activity, receive systemic injections of dexamphetamine, no dexamphetamine stereotypy is seen (Costall et al , 1972a, Fog et al , 1968)
Despite these findings, there are some data which indicate that care is required in the interpretation of the above-mentioned results (a) not all observers have found that neostriatal lesions are effective in suppressing the dexamphetamine stereotypies (Divac, 1972), (b) lesions in other brain structures such as the globus pallidus are more effective in this respect (Naylor et al , 1972), (c) microinjections of dopamine or dexamphetamine into the neostriatum of unpretreated rats are totally ineffective in eliciting the stereotyped patterns, unless very high doses are used (Costall et al , 1972a), and (d) dexamphetamine injections into the globus pallidus are also effective in eliciting the characteristic dexamphetamine stereotypy (Costall et al , 1972a)
Thus, it seems likely that brain dopamine forms at least an important step in the elicitation of the dexamphetamine-induced stereotypies, but it remains to be elucidated whether or not it is only *neostriatal* dopamine which mediates this role

2 4 1 3 The cataleptic model

The above-mentioned models of dexamphetamine and apomorphine have also been used in combination with neuroleptics Neuroleptic drugs are known to reduce the activity of the dopamine system (Anden et al , 1964, 1967a, Carlsson et al , 1963, Janssen, 1967, Nyback et al , 1968, O'Keefe et al , 1970, van Rossum, 1966, 1967, Sharman, 1966, Yeh et al , 1969) It has been demonstrated that systemic injections of neuroleptics elicit a certain form of catalepsy (Bobon et al , 1970, Janssen et al , 1965) Several workers have suggested that this syndrome is mediated by the interference of these compounds with the dopamine-sensitive sites (Anden et al , 1971b, Janssen, 1967, van Rossum, 1967, York, 1972)
The following findings suggest that the catalepsy induced by neuroleptic drugs is mediated by the interaction of neuroleptics with *neostriatal* dopamine (a) when rats pretreated with systemically given reserpine receive bilateral injections of apomorphine (20 ug/5 μl) or dexamphetamine (20 μg/5 ul) into

the neostriatum, the catalepsy is suppressed, and the dexamphetamine stereotypy appears (Fuxe et al , 1970a), (b) when rats pretreated with systemically given dexamphetamine receive bilateral injections of neuroleptics into the neostriatum, the dexamphetamine stereotypy is suppressed, and the catalepsy appears (Costall et al , 1972a, Fog et al , 1968, 1971), and (c) lesions in the neostriatum suppress the effects of systemic injections of neuroleptics (Costall et al , 1971a, b, Fog et al , 1970) The fact that lesions in the globus pallidus can also suppress the catalepsy induced by systemic injections of neuroleptics such as haloperidol (Costall et al , 1971b), however, does not exclude the possibility that other structures are also involved

2 4 1 4 The turning model

A number of experiments have been performed with rats in which the dopamine-balance between both neostriata is disrupted by means of unilateral ablation of one neostriatum or by means of unilateral 6-OH dopamine-induced degeneration of the nigro-neostriatal fibres (Anden, 1965, Anden et al , 1966, 1967b, 1969 1970a, b, c, d, Ungerstedt, 1968, 1971b, c, Ungerstedt et al , 1970) It has been demonstrated that compounds such as dexamphetamine, apomorphine and L-DOPA, which increase dopamine activity, induce turning towards the side on which the neostriatum has been removed (Anden et al , 1966, 1967b, Lotti, 1971)

Anden and his co-workers have suggested that this model can be used for differentiating dopamine-stimulating agents from dopamine-blocking agents This idea is based upon the hypothesis that an increase in dopamine activity on one side of the brain results in turning away from that side, and that decrease in dopamine activity on one side of the brain results in turning towards that side However, it is rather difficult to explain, on the basis of this concept, the fact that unilaterally ablated rats pretreated with reserpine and α-methyl-para-tyrosine turn towards the non-lesioned side (Anden et al , 1966, 1967b) in rats unilaterally deprived of their dopamine-rich neostriatum, inhibition of the dopamine activity on the non-lesioned side can only restore the disrupted balance, but there is no evidence that these substances can induce a change in the disrupted balance in the opposite direction In order to understand these effects, it is of relevance to note that rats and mice with unilateral removal of the neostriatum appear to be quite normal a few days after the operation (Anden et al , 1966, Costall et al , 1972b, Faull et al , 1969, Lotti, 1971, Simpson et al , 1971) apparently, the disrupted balance between both neostriata is somehow counterbalanced Several workers have suggested that there exists a close relationship between dopamine and other brain neurotransmitters (Arnfred et al , 1968, Costall et al , 1971a, Kim et al , 1970, Klawans, 1968, Scheel-Kruger, 1970) It is well known that an artificially induced disruption of acetylcholine activity in the neostriatum can be counterbalanced by an artificially induced change in dopamine activity of the neostriatium and vice versa

(Connor et al , 1967, Costall et al , 1972a, c, d, Lalley et al , 1970) In addition, it has been inter alia found that a disruption of acetylcholine activity induced by cholinergic or anticholinergic drugs is accompanied by a change in the concentration of the dopamine content of the brain (Andén et al , 1971a, Corrodi et al , 1967, Coyle et al , 1969, 1970, Friedmann et al , 1967, Fuxe et al , 1970b, Laverty et al , 1965, O'Keefe et al , 1970, Perez-Cruet et al , 1971, Shellenberger et al , 1971) Although it has been stressed that some of these drugs also directly interfere with the dopamine mechanisms, quite a number of the drugs used only affect the cholinergic mechanisms, so that the change in the dopamine content must be ascribed to a transneuronal relationship between both mechanisms From such data, it seems reasonable to assume that the disappearance of the turning tendency following unilateral degeneration of the dopamine system is due to the counterbalancing effect of one of the non-dopamine neurotransmitter systems The fact that a unilateral increase or decrease in acetylcholine also induces turning to one or the other side strongly supports this suggestion (Costall et al , 1972d, Hull et al , 1967, Stevens et al , 1961) Accordingly, a complete blockade of dopamine activity induced by high doses of reserpine and α-methyl-para-tyrosine may relieve the newly adjusted non-dopamine system so that the animals turn towards the non-lesioned side From these considerations, it becomes apparent that the turning tendency induced by "unknown" drugs cannot be used to indicate the mechanisms of their action On the other hand, it is self-evident that the dopamine balance between both neostriata fulfils an important role in the maintenance of symmetric postures and movements This is supported by the fact that rats pretreated with unilateral injections of 6-OH dopamine into the substantia nigra also turn towards the lesioned side when they are systemically injected with dexamphetamine (Ungerstedt, 1968, Ungerstedt et al , 1970) However, the picture in this case is complicated by the fact that rats pretreated with apomorphine or L-DOPA turn away from the lesioned-side (Ungerstedt, 1971c) In order to explain these findings, it has been suggested that the dopamine-sensitive structures on the 6-OH dopamine-lesioned side have developed a hypersensitivity to dopamine or dopamine-stimulating agents so that these structures are more sensitive to such agents than the dopamine structures on the non-lesioned side accordingly, compounds which directly increase dopamine activity at the dopamine-sensitive sites induce turning away from the 6-OH dopamine-treated side, while compounds which indirectly increase the dopamine activity, by release for instance, induce turning towards the 6-OH dopamine-lesioned side (Ungerstedt, 1971c) However, it will be clear that the objections mentioned above are also valid in this case, if no additional data about the action of "unknown" drugs are available, no conclusion with respect to the mechanisms of action of these drugs can be drawn since disturbances of other neurotransmitter systems could also be responsible for the turning syndrome

In order to present more direct evidence in favour of the functional role of neostriatal dopamine, numbers of workers have studied the effects of neostriatally applied dopamine and related compounds upon the normal behaviour of rats An encouraging start has been made by Ernst et al (1966) Implantations of rather large doses of crystalline L-DOPA (about 200 µg) into the neostriatum of rats resulted, after a delay of 1-2 hr, in intensive compulsive gnawing, the most sensitive site of action was found in the dorsal part of the neostriatum According to Ernst et al (1966), a similar effect was obtained after the implantation of apomorphine Since this effect was not blocked by an α-methyl-para-tyrosine pretreatment, they have suggested that apomorphine might act as a direct dopamine-receptor stimulating agent However, bilateral injections of dopamine (about 200 µg) do not evoke this syndrome but, instead, a severe bradykinesia (Butcher et al , 1972) Recently, Ungerstedt et al (1969) have reported that unilateral microinjections of dopamine (5 ug/5 ul) into the caudate-putamen complex result in turning of the rat contralateral to the side of the injection as soon as the animals recovered from the halothane-N_2O-oxygen anesthesia (10 min after the injection) the turning tendency was shown for a period of 30-60 min Potentiation of this effect was obtained in rats pretreated with nialamide alone or with both nialamide and reserpine A similar effect was also obtained after microinjections of noradrenaline into the same part of the brain In view of the fact that noradrenaline penetrates the caudate-putamen complex in a way similar to that of dopamine, Ungerstedt et al (1969) have concluded that noradrenaline may directly stimulate the dopamine receptors in this complex In contrast to the recent findings of Ungerstedt et al (1969), Dill et al (1968) have reported that microinjections of dopamine (90 µg), noradrenaline (25 µg) or serotonin (50 µg) unilaterally injected into the caudate-putamen complex did not have any effect It has also been shown in our laboratory that unilateral application of 1 0, 10 0 or 50 0 ug dopamine into the neostriatum is ineffective (unpublished data of Malec)

In summary, no clear-cut conclusion can be drawn with respect to the exclusive role of *neostriatal* dopamine in the elicitation of the apomorphine, dexamphetamine and neuroleptic syndromes, whereas much conflicting data have been presented with respect to its role in the so-called turning syndrome

In general, a large number of studies have been employed to investigate the behavioural effects of systemically given drugs which alter the synthesis, binding, release, uptake or degradation of brain serotonin (Aprison et al., 1972; Delorme et al., 1966, Ferguson et al., 1970, Garattini et al., 1965; Harvey et al., 1963, Heller et al., 1972; Lints et al., 1969; Machitelli et al., 1966; Tenen et al., 1967). However, it is difficult to interpret such data in terms of a regional specificity because of its indirect nature. On the other hand, only a very small number of investigations apply to the neostriatal role of serotonin in behaviour. As a matter of fact, only two kinds of research strategies in this field have been employed: studies dealing with brain lesions, and studies dealing with neostriatally administered compounds.

The first mentioned type of approach has shown that a restricted, unilateral lesion of a group of fibres in the dorsomedial area of the cerebal peduncle produces a degeneration of serotonin cell groups in the midbrain and a concomitant depletion of serotonin in the ipsilateral neostriatum (Hassler et al., 1969; Poirier et al., 1966, Poirier et al., 1967; Singh et al., 1967; Sourkes et al., 1966); however, this drop is insufficient to produce strong behavioural effects apart from a slight hypokinesia of the contralateral forelimb. On the other hand, it must be mentioned that such lesions may contribute to severe motor disorders: when they are combined with lesions in the rubro-tegmento-spinal pathway, intensive tremors appear.

During the course of the present studies, more direct evidence in favour of a putative role of neostriatal serotonin has been presented by Hadzovic et al. (1969). He and his co-worker have reported that local application of rather low doses of crystalline 5-hydroxytryptophan (5-HTP: 20 μg), the precursor of serotonin, into the rostroventral part of the neostriatum of rats elicits the above-mentioned L-DOPA gnawing syndrome (see 2.4.1.5.). Apart from the fact that the involved part differs from the part involved in the L-DOPA-evoked gnawing syndrome, it has been shown that inhibition of dopamine synthesis does not inhibit 5-HTP-induced gnawing (Ernst, 1972).

Apart from these indications, no further studies on the *neostriatal* role of serotonin are available.

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CHAPTER 3

INTRACAUDATE ADMINISTRATION OF DOPAMINE IN CATS

3 1. INTRACAUDATE DOPAMINE AND BEHAVIOUR OF CATS

3 1 1 ABSTRACT

Effects of unilateral injections of dopamine (DA) and related compounds into the caudate nucleus of cats via permanently implanted cannulas were measured with the help of a standardized list of behavioural items With the help of this method it could be demonstrated that DA and dexamphetamine induced a highly specific syndrome, while noradrenaline (NA) was ineffective in that sense Different behavioural effects of the DA injections outside and also inside the caudate nucleus were observed Systemically applied haloperidol, a potent blocker of dexamphetamine, could inhibit the behaviour induced by DA or dexamphetamine in the rostromedial part of the caput caudati The reported effects give new evidence for the important role of DA in the caudate nucleus and favours the assumption that haloperidol acts as its competitive antagonist

3 1 2 INTRODUCTION

The localization of dopamine (DA) is mainly restricted to neurons in the substantia nigra, while axon terminals containing dopamine are mainly found in the neostriatum (Andén et al , 1965, Dahlstrom et al , 1964, Hornykiewicz, 1966) There is good evidence that DA-sensitive sites are involved in the central stimulating action of dexamphetamine and cocaine (Fog, 1969, Hanson, 1967, van Rossum et al , 1964) It is well known that neuroleptic drugs like chlorpromazine and haloperidol are potent and selective antagonists of dexamphetamine-like drugs Haloperidol is also able to block the selective DA-induced depressor effect in rabbits and cats (van Rossum, 1966, Yeh et al , 1969) It is attractive to postulate that dexamphetamine inter alia acts by activation of DA-sensitive sites and neuroleptics as DA antagonists, but reliable experiments in order to test this supposition are lacking In this paper the results of a behavioural study will be described in which DA, dexamphetamine and related compounds have been locally introduced into the caudate nucleus of cats

Fifty two cats of either sex, ranging in weight from 2 5 to 3 5 kg, were used Double barrelled, stainless steel cannulas were implanted stereotaxically into both the left and right caudate nucleus at different angles (5, 10 and 15 degrees), and fixed on the skull with acrylic dental cement (the diameter of the guide cannula and injection cannula was 0 8 mm and 0 5 mm respectively) Upon complete recovery from the anesthesia, small quantities (10 0 ul) of drug solutions were injected through the needle which extended into the brain tissue 2 mm below the tip of the permanently embedded cannula The experiments were initiated one week after the operation, and were stopped three months later After completion of the experiments the cats were sacrificed under anesthesia i e perfused through the heart with saline and subsequently with 10% formaldehyde solution The brains were removed and fixed in 4% formaldehyde solution For the precise identification of the contact locations, 40 μ frontal sections of the brain were made and stained with acidified 0 25% cresyl violet With the help of the stereotaxic atlas of Jasper (1954) four main locations were distinguished the rostral part of the caput caudati (co-ordinates A=16-17, L=3-6 and H=14-16, 13 cats), the rostromedial part of the caput caudati (co-ordinates A=14-15, L=4-6 and H=14-17, 34 cats), the tail of the caudate nucleus (co-ordinates A=11-12, L=5-6 and H=15-17, 4 cats) and the internal capsule (co-ordinates A=11-12, L=8-9 and H=12-14, 4 cats) Once a week the cats received one 10 0 μl injection of the following substances saline (NaCl 9 0 ug/ul), dopamine-HCl (DA 0 20-12 00 μg/μl), L-3 4-dihydroxyphenylalanine-HCl (L-DOPA 0 19-16 00 μg/ul), noradrenaline-HCl (NA 1 00-6 00 μg/μl) and dexamphetamine-H_2SO_4 (0 42-14 40 μg/μl), all drugs were dissolved in saline and adjusted to pH 4-5 Eighteen animals received an intraperitoneal injection of haloperidol (100-200 μg/kg) 45 min prior to the administration of DA or dexamphetamine (haloperidol was dissolved in propyleneglycol)

The spontaneously occurring and induced behaviour was stored on videotape by using a closed TV circuit The behaviour was analysed from the tapes over periods of 5 min (time-block), and recorded on standard ethograms (table 1) The observation period of 45 min was divided into nine time-blocks, three before and six after the injection During each minute the presence or absence of the items was recorded whereas specific symbols were listed for the items 8, 10, 13, 18, 19 and 34, at the end of each time-block, a noise stimulus was presented The 15 min period preceding the injection was used as control-period Half an hour before the control-recordings, the cat was placed in the observation cage (75 x 75 x 80 cm) to reduce its exploration activity

As the consequence of two preliminary sessions of one hour each in the testcage, the animals had a very low activity-level during their pre-trial habituation period Accordingly, the following scores were arbitrary chosen

table 1

Ethogram of the cat: the presence or absence of the listed items was recorded during each minute of the 45 min observation period; special symbols were listed for the items 8, 10, 13, 18, 19 and 34*.

"Dynamic Units"	"Static Units"	"Sense Units"	"Specific Units"	
1. Lying	8 Head movement	14. Miosis	21. Chewing	29 Trampling
2. Sitting	9. Neck tension	15. Mydriasis	22. Licking	30. Mouth-opening
3 Standing	10 Tail movement	16. Ptosis	23. Swallowing	31. Tongue extrusion
4 Walking	11. Forelimb extension	17. Nictitating membrane	24. Sniffing	32. Piloerection
5. Moving	12. Hindlimb extension	18. Eye-opening	25. Miaowing	33. Convulsion
6 Exploring	13. Posture	19. Ear-movement	26. Gasping	34. Respiration rate
7. Springing		20 Clawing	27. Staring	35. Urination
			28 Swinging	36. Defecating
				37. Cleaning

* "Response Units" are the items 1-37, recorded during a noise stimulus presented at the end of each time-block (5 min).

0 = 0/time-block,
1 = 1/time-block (low frequency),
2 = 2-4/time-block (intermediate frequency),
3 = > 4/time-block (high frequency)

When behavioural items were alternately directed towards both sides (head movements, limb movements), an additional score indicating the preferential side was given when the frequency of an item, directed towards one side, exceeded 75% of the total frequency of that item, this was scored as h (injected side) or c (non-injected side), in the remaining cases, the absence of any preference was scored as a (alternately)

3 1 4 RESULTS

3 1 4 1 Dose-response dependency of L-DOPA

In general, the symptoms appeared at the end of the fourth time-block and had a nearly constant frequency during the fifth period, while they disappeared during the following periods The application of 10 0 µg L-DOPA into the rostromedial part of the caput caudati resulted in a strong reduction of the "dynamic units" except lying and in a substantial change in the "static units" nearly all the time the cats were lying and showed frequent turning of the head, contralateral to the side of the injection, while the limbs were flexed in an abnormal way, sometimes the cats extended the contralateral forelimb and/or the homolateral hindlimb Although the animals showed an increased alertness (high frequency of the "response units"), ptosis, miosis, contralateral turning of the eye-balls, fluttering of the contralateral ear and contractions of the contralateral facial muscles were present too When the above-mentioned effects, called the "contralateral" syndrome, had a low and high frequency, especially of the contralateral movements, the behaviour was classified as type 2 and type 3 respectively (table 2) Increase of the L-DOPA concentration resulted in a shift from type 2 to type 5, mainly marked by the shift of the direction of the head movements from the contralateral side (types 2 and 3) to the homolateral side (type 4 the so-called "ipsilateral" syndrome) and, finally, to both sides (type 5) The dose-response relation of L-DOPA is summarized in table 3 No differences were observed between injections given through cannulas which were implanted at different angles

3 1 4 2 DA, NA, dexamphetamine and saline

The application of 10 0 µg of DA into the rostromedial part of the caput caudati had essentially the same effects as L-DOPA However, during the first two time-blocks some animals turned continuously to the contralateral side, while during the following periods they did not show any preferential direction to

table 2

Frequencies of some items of the behavioural types induced by caudate application of saline (NaCl type 1), L-DOPA, dopamine and dexamphetamine (types 2-5) and noradrenaline (type 6) in cat no 4691, the dose-type relation of L-DOPA, dopamine and dexamphetamine is shown in table 3 The low, normal and high frequencies are indicated as follows 1 (1/time-block), 2 (2-4/time-block) and 3 (> 4/time-block), while the side of occurrence of the items is shown by a (both sides), h (injection side) and c (opposite to the injection side), vertical movements are indicated with I. Note the shift from contralateral to homolateral in types 2-4

Behavioural types	1	2	3A	3B	3B	3C	3C	4A	4B	4B	5	6
Time-block no	5	5	5	4	5	4	5	5	4	5	5	5
'Dynamic units"												
Lying	2	2	3	0	3	0	3	3	0	3	3	3
Sitting	2	1	1	1	1	1	1	0	1	0	0	0
Standing	2	1	1	1	1	1	1	0	1	0	0	0
Walking	2	1	1	3c	1	3c	1	1	3h	1	0	0
Moving	2	1	1	1	1	1	1	0	1	0	0	0
Static units"												
Head movement	3a	1c	3c	3c	3a	3I	3c	3h	3h	3a	3a	0
Forelimb extension	0	1c	2c	0	2c	3I	2c	2h	0	2h	2a	0
Hindlimb extension	0	1h	2h	0	2h	0	2h	2c	0	2c	0	0
"Specific units"												
Tongue extrusion	1	3	3	2	3	2	3	0	0	0	0	0
Licking	2	3	2	2	2	2	2	0	0	0	0	0
'Sense units"												
Ptosis	0	1c	3c	0	3c	0	3c	3h	0	3h	0	0
Miosis	0	3	3	3	3	3	3	0	0	0	0	0
Mydriasis	0	0	0	0	0	0	0	3	3	3	0	0
Ear-movement	2a	2a	2c	2c	2c	2c	2c	2h	2h	2h	0	0
"Response units"												
Low											x	x
Normal	x							x	x	x		
High		x	x	x	x	x	x					

turn their heads· therefore, this behaviour was classified as type 3B (table 2). The above-mentioned shift of behavioural types, induced by different L-DOPA doses, could be similarly produced by different DA doses (table 3).
The application of 10.0 μg of dexamphetamine into the same part of the brain resulted in vertical head movements and alternate lifting up of the forelimbs during the fourth time-block, while at the same time an increase in the "dynamic units" was shown. During the fifth and following periods the dexamphetamine behaviour was essentially the same as the L-DOPA behaviour; the overall behaviour to 10.0 μg of dexamphetamine was classified as type 3C (table 2). Furthermore, dexamphetamine showed the same dose-response dependency as L-DOPA or DA (table 3).
The application of 10.0 μg of NA into the rostromedial part of the caput caudati caused the following behaviour: the "dynamic units" like moving, standing, sitting and walking disappeared, while the "static units" were characterized by the absence of limb and neck tonus: the cat was drowsy and did not show the normal reaction to the noise stimulus, while turning of the head and movements of the limbs were totally absent. This kind of behaviour was classified as type 6 (table 2).
Apart from the first minutes saline did not show any effect upon the behaviour.

3.1.4.3. Antagonism

Haloperidol alone produced the following syndrome. a strong reduction of the frequency in all items except lying, however, the "dynamic units" did not disappear and the "response units" were still present. Haloperidol abolished the behavioural effects of low doses of DA and dexamphetamine (2 0-10.0 μg): the cats showed predominantly the behavioural effects induced by haloperidol alone.
The effects of larger doses (20.0-60.0 μg) of dexamphetamine and DA were reduced by haloperidol, and the haloperidol effect disappeared. In the presence of haloperidol the behavioural effect of 20 0-60.0 μg DA was equivalent to a dose of 10.0 μg when given alone. There was a mutual antagonism between DA and dexamphetamine on the one hand and haloperidol on the other hand.

3.1.4.4. The caudate nucleus

All above-mentioned effects could be produced by application of the drugs into the rostromedial part of the caput caudati. The effects of DA or dexamphetamine injections into the tail were not uniform in all animals. However, most animals (75%) showed effects similar to the effects of rostromedial caudate applications; these cats showed the abnormal items about 10 min

table 3

Behavioural types, induced by unilateral caudate injections in cats, related to different doses The types refer to table 2. Note that type 6 only occurs in the noradrenaline column

L-DOPA dose µg/10 0 µl	type	(exp)	dopamine dose µg/10 0 µl	type	(exp)	dexamphetamine dose µg/10 0 µl	type	(exp)	noradrenaline dose µg/10 0 µl	type	(exp)
1 9	2	(2)	2	2	(8)	4 2	3c	(2)	10 0	6	(8)
7 0	3a	(2)	5	2	(4)	9 2	3c	(2)	20 0	6	(4)
10 0	3a	(2)	,,	3a	(8)	10 0	3c	(8)	30 0	6	(4)
15 0	3a	(4)	,,	3b	(6)	13 7	3c	(2)	60 0	6	(4)
19 8	3a	(6)	10	3a	(14)	15 0	4a	(2)			
20 0	3a	(4)	,,	3b	(4)	20 0	4a	(2)			
,,	4a	(4)	20	3a	(8)	,,	4b	(2)			
22 0	3a	(2)	,,	3b	(2)	25 0	4a	(2)			
39 6	4a	(4)	25	3a	(2)	40 0	5	(2)			
40 0	4a	(2)	,,	4a	(8)	80 0	5	(2)			
60 0	4a	(2)	40	5	(2)	108 0	5	(2)			
80 0	4a	(2)	60	5	(6)	126 0	4b	(2)			
,,	4b	(2)	120	5	(4)	144 0	4b	(2)			
84 0	5	(2)							NaCl (saline)		
96 0	5	(2)							dose ug/10 0 µl	type	(exp)
150 0	5	(4)									
160 0	5	(2)							90 0	1	(20)

later than the cats with cannulas in the rostromedial part of the caput. The injections into the rostral part of the caput caudati gave the same effects as they did into the rostromedial part, although the latency was increased to about 25 min. The animals with the cannulas in the internal capsule showed strong contralateral effects of the limbs, ears, eyelids and facial muscles a few minutes after the injection of DA or dexamphetamine, but about 25 min later they showed the contralateral turning of the head.

3 1 5 DISCUSSION

DA application into the caudate nucleus of cats has been found to produce a highly specific behaviour, that differs from the behaviour induced by NA. In rats Ungerstedt et al. (1969) have found that caudate application of DA induces the same effect as NA. In view of the anatomical differences, it could be a species-difference. It is important to report that all induced effects occurred after a latency of about 5 min. With reference to the supposed function of DA in the caudate nucleus (Hornykiewicz, 1966), three possible causes will be discussed·
A. A biochemical delay (if the trigger of the behavioural response is a DA metabolite, the rate of formation of this metabolite could be limiting)
B. A diffusion delay (if the reactive sites of DA lie outside the caudate nucleus, the diffusion to these sites could be limiting).
C. A functional delay (if the trigger of the response is a special balance of several neurotransmitters, the time to adjust the new balance could be limiting).
The existence of a biochemical delay can be rejected by the following facts and considerations:
(a) During rest a large amount of DA is released in the caudate nucleus (McLennan, 1964).
(b) The high concentration of DA in the caudate nucleus is mainly stored in synapses, i.e. in the storage sites of neurotransmitters (Dahlstrom et al., 1964).
(c) There is strong evidence, that the caudate nucleus receives DA-containing nerve connections from the substantia nigra (Andén et al., 1965)
(d) DA has a specific depressant effect on the neuronal activity of a major part of the caudate neurons (Bloom et al , 1965, Connor, 1968; Herz, 1966, 1968; York, 1967).
These four facts favour the assumption of an important function of DA itself (see 2.4.1.).
Moreover:
(e) In our experiments the DA and NA effects have been proved to be totally different, while the effects of L-DOPA, the precursor of DA, have been found to be similar to those of DA.
Furthermore, the dexamphetamine effects resemble the DA effects. Although there is not enough evidence to determine the whole workings-spectre of

dexamphetamine, it is believed to release DA and NA (Carlsson et al , 1966) our results and those of McKenzie (1968) indicate that it interferes mainly with DA in the caudate nucleus This is in agreement with other observations (Fog et al , 1967, 1968, 1969, Hanson, 1967, Randrup, 1966a, b)
(f) Haloperidol, a peripheral inhibitor of DA blood pressure effects (van Rossum, 1966, Yeh et al , 1969) antagonises the central DA effect This counteracting effect appears to be competitive since high doses of DA overcome the suppression the competitive nature has already been shown for the DA-induced vasodilatation in the renal beds of the dog (Yeh et al , 1969)

All the above-mentioned arguments validate the hypothesis that the observed behaviour is due to an activation of DA-reactive sites The possibility of a diffusion delay could be rejected too
(a) The described effects of DA show a remarkable resemblance to the effects of electrical stimulation of the caudate nucleus Akert et al (1951) reported the following effects of caudate stimulation in cats inactivation and raising of the overall threshold for external stimuli, ptosis, miosis, abnormal position of the limbs, low respiration rate and contralateral effects Although they argued that the contralateral effects are the results of capsule stimulation as a consequence of irradiation, other authors (Forman et al , 1957) doubt this From our experiments we can conclude that the contralateral movements of the head seem to arise in the caudate nucleus (in the caudate these effects appeared within 5-10 min and in the capsule within 20-25 min after the injection) Moreover, the other stimulation effects are quite the same as our described responses to 10 0 µg of DA
(b) Not only outside, but also inside the caudate nucleus we have observed a strong difference in latency
(c) Accidental lesions in the caudate nucleus of two cats resulted in the ablation of the specific responses
Apart from the earlier mentioned facts, these facts support the assumption that the reactive sites lie within the caudate nucleus In fact, another cause of the long latency must exist We should like to discuss the third possibility the functional delay
Several authors have already suggested that there could be an acetylcholine-dopamine balance (Fahn et al , 1968, Goldstein et al , 1969, Shute et al , 1967). Indeed, a major part of caudate neurons are acetylcholine-sensitive and iontophoretic applied acetylcholine induces an increase in the neuronal activity (McLennan et al , 1966)
In fact, antagonism of acetylcholine by atropine is not without effect on the turnover of DA (Cox et al , 1970, O'Keefe et al , 1970) and drugs like reserpine, α-methyl-meta-tyrosine and diethyl-dithiocarbamic acid, which have in common the ability to decrease tissue catecholamine concentrations, inhibit the effects of oxotremorine which induces an increase in brain acetylcholine (Cox et al , 1970) These facts indicate that the balance of neurotransmitters acts as the

trigger for behavioural responses This means that a disrupted balance itself, or a new adjusted balance, could be the trigger for the observed effects In view of these comments the time to adjust to a new balance might cause the functional delay Although the precise function of DA is not yet solved, we have found new indications for the existence of DA-sensitive sites within the caudate nucleus Future work will attempt to alter the various parameters by means of combinations of different drugs, in this manner it is hoped to differentiate the effects of single neurotransmitters from those of several neurotransmitters in the caudate nucleus upon the behaviour of cats

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3 2 THE SPECIFICITY AND ANTAGONISM OF THE DOPAMINE-INDUCED EFFECTS

3 2 1 ABSTRACT

Behavioural effects elicited in cats by apomorphine, dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxytyramine and procaine were measured with, and without pretreatment with locally applied α-methyl-paratyrosine (α-MT) and haloperidol All drugs were unilaterally injected into the rostromedial part of the caput caudati It could be demonstrated that the syndrome induced by dexamphetamine, apomorphine, DA and 3-methoxytyramine is "dopamine-specific" It was shown that haloperidol acts in a competitive way at the level of the DA-sensitive sites The finding of competitive antagonism between α-MT and haloperidol on the one hand and dexamphetamine and apomorphine on the other hand support the hypothesis that both substances have at least a direct action upon the DA-sensitive sites
Furthermore, it was shown that the behavioural effect of 3-methoxytyramine was blocked by haloperidol and α-MT in a non-competitive way the 3-methoxytyramine effects, therefore, appear to be dependent on the presence of DA and/or free DA-sensitive sites The similarity of haloperidol and procaine effects and the diametrically opposite effects of DA are discussed in relation to the DA function in the caudate nucleus

3 2 2 INTRODUCTION

It is well known that intraperitoneally injected amphetamine induces a stereotyped behaviour in several species such as rats, cats and monkeys (Randrup et al , 1967)
Biochemical and anatomical evidence indicates that these stereotypies have some relation to the dopamine (DA) system of the basal ganglia (Munkvad et al , 1968) However, the greater part of the direct evidence is based upon experiments with rats, in which microinjections of dexamphetamine and DA into the neostriatum and lesions in this nucleus have been performed (Fog et al , 1970) Recently, it has been found that, indeed, DA locally introduced into the rostromedial part of the caput caudati of cats induces remarkable changes in the behaviour of cats (Cools et al , 1970, see 3 1)
The aim of the present investigation was to determine the specificity of the DA-induced effects in cats It has been previously shown that unilateral injections of DA, its precursor L-3,4-dihydroxyphenylalanine (L-DOPA) and dexamphetamine induced a characteristic syndrome, marked by changes in the frequency of activities such as walking and cleaning, and by characteristic movements of the head, limbs, facial muscles, ears and eyes, noradrenaline (NA) was ineffective in that sense (Cools et al , 1970, see 3 1)

In fact, the metabolic degradation of DA in the basal ganglia does not involve the formation of NA (Vogt, 1965), but rather the formation of intermediates such as 3-methoxytyramine (which is believed to be located predominantly in the cytoplasm of extraneuronal cells (Iversen et al , 1966) and 3,4-dihydroxy-phenylacetic acid (DOPAC, which is found in both mitochondrial and/or microsomal fractions (Youdim et al , 1968)) The significance of the findings of the DA effects needs to be determined with respect to the effects induced by these intermediates As a result of turnover studies of DA (Anden et al , 1970), a feedback mechanism upon DA synthesis has been postulated Although the physiological role of the intermediates in this mechanism is unknown, such a postulate sets the problem of determining the effects induced by DA or its metabolites alone, without interference by DA synthesis, release or re-uptake systems In the present study α-methyl-para-tyrosine (α-MT), an inhibitor that specifically blocks the in vivo hydroxylation of tyrosine (the first step in DA synthesis (Spector et al , 1965)), was utilized to examine this problem
In view of the DA effects of dexamphetamine (Cools et al , 1970, see 3 1 , Fog et al , 1970) and apomorphine (Anden et al , 1967, Ernst et al , 1966), a parallel study of both substances following a pretreatment with a DA synthesis inhibitor was included in order to test their direct "receptor-stimulating" action *In a previous report (Cools et al , 1970, see 3 1) it has been shown that* intraperitoneally injected haloperidol, a peripheral inhibitor of DA effects and a selective antagonist of dexamphetamine-like drugs, acts as a competitive antagonist of the DA-induced effects The present study deals with the antagonistic effects of locally applied haloperidol in order to rule out the possible influence of haloperidol upon caudate-stimulating or -inhibiting brain nuclei
In view of the suggestion that DA is an inhibiting neurotransmitter and acts as a de-inhibitor of the normally exerted caudate inhibition (Hornykiewicz, 1966, van Rossum et al , 1964), it seems reasonable to assume that caudate lesions should induce effects similar to the DA-induced effects In order to analyse its function in this respect, reversible lesions were made with the help of procaine

3 2 3 METHODS

The subjects used were male cats, ranging in weight from 2 5 to 3 5 kg Double barrelled, stainless steel cannulas were implanted stereotaxically into the left and right caudate nucleus (co-ordinates A=14-15, L=4-6, H=14-17) Upon complete recovery from the anesthesia, small quantities (10 0 ul) of drug solutions were injected through the injection needle which extended into the brain tissue 2 mm below the tip of the permanently embedded cannulas, the experiments were initiated one week after the operation Further details of the procedure can be found elsewhere (Cools et al , 1970, see 3 1) The following substances were injected saline (control), dopamine-HCl (DA), 3-methoxytyr-

amine-HCl, noradrenaline-HCl (NA), 3,4-dihydroxyphenylacetic acid (DOPAC), dexamphetamine-H_2SO_4, apomorphine-HCl, haloperidol, DL-α-methyl-para-tyrosine (α-MT) and procaine-HCl, all drugs were dissolved in saline and adjusted to pH 4-5 except for α-MT, which was suspended in saline In each test six animals (12 injection-loci) were used

3 2 4 RESULTS

3 2 4 1 3-methoxytyramine and DOPAC

The unilateral application of 10 0 µg of 3-methoxytyramine into the rostromedial part of the caput caudati resulted in the following behaviour during the fourth time-block vertical head movements, alternately lifting up of the forelimbs and an increase in the "dynamic units" like springing and exploring, during the fifth time-block frequent contralateral turning of the head, abnormally flexed limbs, extensions of the contralateral forelimb, contralateral turning of the eye-balls, fluttering of the contralateral ear, contractions of the contralateral facial muscles and mydriasis The animals showed alternately periods of rest, marked by low frequency of the abnormal motor responses and increased alertness (high frequency of the response items), and periods of activity, marked by high frequency of the abnormal motor responses and absence of any orienting response, this rhythm of rest and activity increased during the fourth time-block and decreased during the sixth time-block Increase of the 3-methoxytyramine concentration from 10 0, 20 0, 30 0, 40 0 to 60 0 µg respectively resulted in the increase in the frequency of these abnormal motor responses In contrast, the application of 10 0, 20 0, 30 0, 40 0, 50 0 or even 60 0 µg DOPAC did not result in any disturbance of the normal behaviour, these data are summarized in table 4 In order to compare these data with previously reported effects of DA, NA and saline, they are summarized in the same table It should be mentioned that the rhythm of rest and activity was also present in the experiments with DA, L-DOPA and dexamphetamine, although it was not reported extensively (see 3 1 4)

3 2 4 2 Apomorphine

The application of 0 6 µg apomorphine had essentially the same effects as 10 0 µg 3-methoxytyramine, increase of the apomorphine concentration from 0 6, 1 3, 2 5 to 5 0 µg also resulted in an increase in the frequency of the abnormal motor responses However, a dose of 15 0 µg apomorphine resulted in a shift in the direction of the movements from the contralateral side to the homolateral side

table 4

Frequencies of some items of the behavioural syndromes induced by caudate application of saline (90.0 μg NaCl), dopamine and its metabolites (10.0 μg each) in cat no 4895. The low, normal and high frequencies are indicated as follows: 1 (1/time-block), 2 (2-4/time-block) and 3 (>4/time-block), while the side of occurrence of the items is shown by: a (both sides), h (injection side) and c (opposite to the injection side), vertical movements are indicated with l

COMPOUND	saline		dopamine		noradrenaline		DOPAC		3-methoxytyramine	
Time-block no	4	5	4	5	4	5	4	5	4	5
"Dynamic units"										
Lying	2	2	3	3	2	3	2	2	1	3
Sitting	2	2	1	1	1	0	2	2	3	1
Standing	2	2	1	1	1	0	2	2	3	1
Walking	2	2	1	1	1	0	2	2	3	1
Moving	2	2	1	1	1	0	2	2	3	1
Exploring	0	0	0	0	0	0	0	0	2	0
Springing	0	0	0	0	0	0	0	0	3	0
"Static units"										
Head movement	3a	3a	3a	3c	2a	0	3a	3a	3l	3c
Forelimb extension	0	0	0	2c	0	0	0	0	3l	2c
Hindlimb extension	0	0	0	2h	0	0	0	0	0	2h
"Specific units"										
Tongue extrusion	1	1	3	3	3	0	0	0	2	3
Licking	2	2	3	1	3	0	2	2	3	1
Sniffing	2	2	3	1	3	0	2	2	3	1
Cleaning	2	2	3	1	3	0	2	2	3	1
"Sense units"										
Ptosis	0	0	0	3c	0	0	0	0	0	3c
Miosis	0	0	0	3	0	0	0	0	0	0
Mydriasis	0	0	0	0	0	0	0	0	0	3
Ear-movement	2a	2a	2a	2c	2a	0	2a	2a	2a	2c
"Response units"										
Low						x				
Normal	x	x	x		x		x	x	x	
High				x						x

3.2.4 3. α-MT

The unilateral application of 20 0 µg α-MT resulted in homolateral turning of the head and movements of the homolateral forelimb and/or the contralateral hindlimb after about 25 min

Apart from the increased cleaning and licking activity on the homolateral side of the face, the homolateral forelimb and the contralateral hindlimb, the induced movements were difficult to observe, since the animal, apparently forced to execute an irrelevant movement, immediately performed a normal motor pattern of which the elicited movement formed the initial phase, although the same held true for each caudate-induced effect, the occurrence of this masking effect was much stronger in the case of α-MT injections.

When α-MT was given 25 min prior to DA, the effects could be summarized as follows: a normal effective dose of 10 0 µg DA did not induce any change in the pretreatment behaviour, while doses of 20 0 and 30 0 µg suppressed the α-MT behaviour and induced some characteristics of the DA syndrome: contralateral turning of the head and contralateral extensions of the forelimb; high doses of DA (40 0 and 50 0 µg) totally surmounted the pretreatment behaviour, and induced the original DA effects (fig 1)

The metabolites, NA, DOPAC and 3-methoxytyramine (doses: 10 0, 20 0, 30 0, 40 0 and 50.0 ug), could not change the pretreatment behaviour, and even in high doses (60 0 µg) these substances were ineffective in surmounting the α-MT effects (fig 1)

On the other hand, dexamphetamine and apomorphine had the same dose-response dependency as DA a normal effective dose (10 0 and 0.6 µg respectively) induced no change in the pretreatment behaviour, while intermediate doses (30 0 and 5 0 ug respectively) resulted in a partial suppression of the α-MT effect and in the induction of some characteristic features of the original syndrome; high doses (60 0 and 30 0 µg respectively) completely produced the characteristic behaviour of dexamphetamine and apomorphine (fig 1)

3.2.4.4. Haloperidol

A unilateral injection of 25 0 ug haloperidol induced the same behaviour as 3-methoxytyramine, however, all unilateral effects, induced by haloperidol, were shown on the homolateral side. homolateral turning of the head, homolateral turning of the eye-balls, homolateral ptosis, fluttering of the homolateral ear and contractions of the homolateral facial muscles Apart from the absence of the increased alertness during the periods of rest, as mentioned for 3-methoxytyramine, the rhythm of rest and activity was also present The latency of the induced effect was even shorter than the latency of the dopamine-induced effect

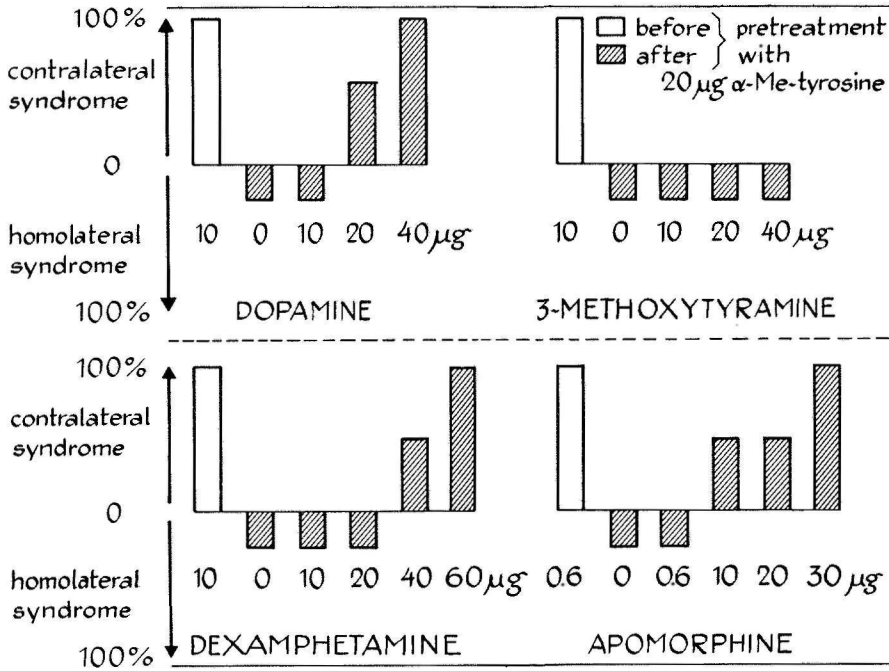

fig 1. The behavioural effects of intracerebral injections (10.0 μl) of various doses of dopamine, 3-methoxytyramine, dexamphetamine and apomorphine into the caput nuclei caudati rostromedialis of cats after the intracaudate application of α-MT (20.0 μg/10.0 μl) given 25 min earlier.

When haloperidol was given 5 min prior to dosing with 10.0 or 20.0 μg DA, the pretreatment behaviour was unchanged. However, high doses of DA (30.0, 40.0 and 50.0 μg) induced the original DA-induced behaviour apart from the fluttering of the ear, the turning of the eye-balls and the unilateral ptosis (fig 2).

Application of NA, DOPAC or 3-methoxytyramine even in high doses (60.0 μg) following a pretreatment with haloperidol did not induce any change in the pretreatment effects (fig 2). Otherwise, dexamphetamine and apomorphine showed the same dose-response dependency as DA: a normal effective dose (10.0 and 0.6 μg respectively) induced no change in the pretreatment behaviour, while higher doses (40.0 μg) produced the original dexamphetamine and apomorphine behaviour apart from the unilateral effects of the face (fig 2).

3 2 4 5 Procaine

The unilateral application of 10 0 ug procaine induced homolateral movements and effects of the head, limbs, facial muscles, eyes and ears after a latency of about 5 min, no distinguishable differences between procaine and haloperidol application were observed When 10 0 ug DA was injected into the right caudate nucleus simultaneously with 10 0 ug procaine into the left caudate nucleus, a remarkable reinforcement of the syndrome was observed the animal dragged itself along with shaky knees in small circles to the left, while the head was rotated more than 180 degrees in this direction, frequent twitchings on the left side of the face were observed

3 2 5 DISCUSSION

In several reports (Fog et al , 1970, Munkvad et al , 1968) it has been suggested that the behavioural syndrome induced by dexamphetamine is mediated by the DA mechanism in the neostriatum This suggestion is based mostly upon the facts that dexamphetamine-induced effects in rats were abolished by an α-MT pretreatment on the one hand and these effects were not inhibited by a diethyldithiocarbamic acid pretreatment on the other hand (Munkvad et al , 1968, Randrup et al , 1966) However, NA effects and DA effects following microinjections into the neostriatum of rats have been shown to be similar (Ungerstedt et al , 1969) In contrast, these differences exist in cats as mentioned in the introduction

The results of this investigation give evidence that not only NA, but also the oxidative de-amination product of DA, DOPAC, is ineffective, the case of the O-methylation product, 3-methoxytyramine, is more complicated Although its application in low doses appeared to be effective, higher doses did not induce the change, which could be induced by higher doses of DA, as previously mentioned (Cools et al , 1970, see 3 1 4) Furthermore, α-MT pretreatment or haloperidol pretreatment inhibited the induced effect as a whole Since 3-methoxytyramine was effective only in the presence of a normal DA metabolism, the so-called "dopamine effect" following low doses of 3-methoxytyramine, has to be considered as an indirect effect this metabolite seems to influence the DA synthesis, its release or its re-uptake system

In conclusion, the ineffectiveness of DA metabolites and the fact that only high doses of DA could break through the α-MT pretreatment, give solid evidence in establishing DA as the inducer of the elicited effects

Secondly, apart from the similarity between the DA, dexamphetamine and apomorphine findings, the effectiveness of the last two substances following inhibition of DA synthesis argues strongly in favour of their direct "receptor-stimulating" action With respect to apomorphine, this suggestion is in

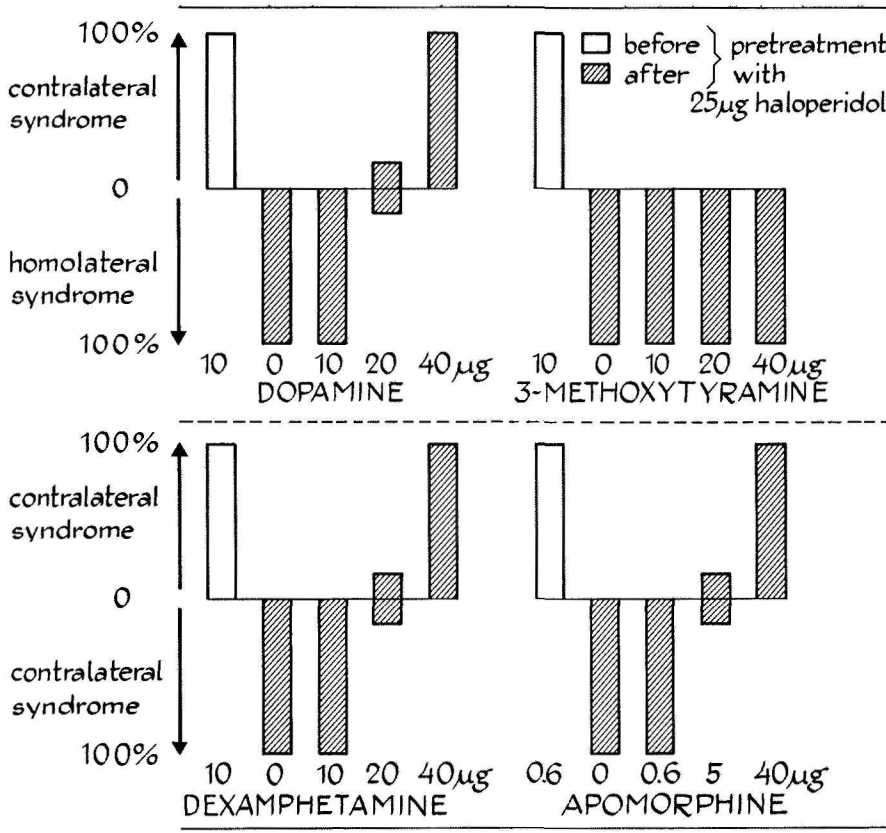

fig 2. The behavioural effects of intracerebral injections (10.0 µl) of various doses of dopamine, 3-methoxytyramine, dexamphetamine and apomorphine into the caput nuclei caudati rostromedialis of cats after the intracaudate application of haloperidol (25.0 µg/10.0 µl) given 5 min earlier.

agreement with previously reported experiments with rats, in which apomorphine was still effective after inhibition of the synthesis-pool of DA and depletion of the reserpine-sensitive pool of DA (Ernst, 1967). With respect to dexamphetamine, the discussion is still going on, since its workings-spectre is more complicated, although its effectiveness following pretreatment with reserpine as well as with α-MT (Stolk et al., 1970) point to its direct "receptor-stimulating" action.

Thirdly, our study with haloperidol supports the theory that neuroleptics such as haloperidol are at least antagonists of the DA mechanism of the neostriatum

(Fog et al , 1968, 1970), the competitive character not only with respect to DA, but also with respect to the dexamphetamine and apomorphine effects strongly indicate that haloperidol acts on the level of the DA-sensitive sites in the caudate nucleus of cats These data agree with the experiments, in which lesions in the neostriatum abolished the neuroleptic-induced catalepsy in rats (Fog et al , 1970)

Suggestions have been made that DA is a postsynaptic inhibitor, since many neurophysiological observations have shown that inhibition is the most consistent effect of DA on the activity of single neurons of the brain (Herz et al , 1966) In fact, the depressant actions can be explained in two ways (a) activation of inhibiting neurons or (b) inhibition of facilitating neurons Keeping in mind these two possibilities, one may now turn to the effects of DA and electrical stimulation on the one hand and the effects of lesions, haloperidol and procaine on the other hand unilateral lesions in the caudate nucleus of cats and of other mammals result in homolateral movements and effects (Gijbels, 1965, Martin, 1966, White et al , 1954), similar effects are induced by unilateral application of haloperidol or the local anesthetic procaine as shown in the present experiments In contrast, DA application and electrical stimulation results in the opposite behaviour (see 3 1 4 , Forman et al , 1957, Laursen, 1963) *These data indicate that DA may primarily cause activation*, since lesion or local anesthesia abolishes the DA effect In view of these observations, it can be postulated that DA causes only activation of inhibiting neurons and not inhibition of facilitating neurons

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3 3 THE INVOLVEMENT OF INTRACAUDATE DOPAMINE IN ATHETOID AND CHOREIFORM HYPERKINESIAS

3 3 1 ABSTRACT

Behavioural changes resembling human athetoid and choreiform hyperkinesias were produced by unilateral injections of L-3,4-dihydroxyphenylalanine (L-DOPA), dopamine (DA), 3-methoxytyramine and dexamphetamine into the rostromedial part of the caput caudati of cats, saline, noradrenaline (NA) and 3,4-dihydroxyphenylacetic acid (DOPAC) were ineffective Pretreatment with the tyrosine hydroxylase inhibitor, α-methyl-para-tyrosine (α-MT), blocked the effects induced by L-DOPA, DA and dexamphetamine in a competitive way, the 3-methoxytyramine effect was blocked in a non-competitive way Applications of the active compounds into the anteroventral part of the caput caudati were either ineffective or less effective
The hypothesis is put forward that normally DA-sensitive sites are involved in the manifestation of choreo-athetoid movements The implications of these findings are considered in view of the efficacy of L-DOPA and α-methyl-DOPA in Parkinson's disease and Huntington's chorea, respectively In addition, our data are discussed in the light of the recent finding that lesions restricted to the anteroventral part of the caput caudati also result in these hyperkinesias

3 3 2 INTRODUCTION

Since Ehringer and Hornykiewicz reported in 1960 that the concentration of dopamine (DA) in the neostriatum and globus pallidus is reduced in parkinsonism, considerable interest has developed in the neurochemistry of the underlying disorder At the present time, the introduction of L-3,4-dihydroxyphenylalanine (L-DOPA) appears to be the most important advance in the treatment of Parkinson's disease (Klawans et al , 1970b) Long-term L-DOPA therapy improves the bradykinesia, rigidity, loss of postural reflexes and, to a lesser extent, the tremor of parkinsonism (Cotzias et al , 1969, Yahr et al , 1969) In view of the essential role of DA in the caudate nucleus (Hornykiewicz, 1966), it is generally accepted that the therapeutic efficacy of L-DOPA is due to the replacement of DA in the basal ganglia by exogenous DA derived from L-DOPA (Klawans, 1968)
However, L-DOPA treatment is not without side-effects In a significant number of patients extremely severe choreo-athetoid movements are seen after long-term treatment (Papavasiliou et al , 1969, Yahr et al , 1969) Choreo-athetoid movements are generally imputed to structures such as the subthalamic nucleus, putamen, nucleus accumbens septi and brachium conjunctivum Papavasiliou et al (1969) therefore suggested that the side-effects

secondary to long-term treatment of L-DOPA only develop when excesses of DA enter neurons from which they are ordinarily excluded, their arguments are in favour of normally DA-insensitive sites as the target sites of these side-effects

On the other hand, in a report describing the behavioural effects of small lesions in cats, Liles and Davis (1969a) provided the information that the caudate nucleus itself is involved in choreo-athetoid hyperkinesias

In view of these findings the hypothesis may be put forward that the normally DA-sensitive sites are also involved as the target sites of the choreo-athetoid movements

In former experiments it was shown that DA, administered unilaterally into the caudate nucleus of cats, induced a characteristic behaviour, marked by a decrease in "specific units" such as licking and cleaning, by a decrease in "dynamic units" such as standing and walking and by specific movements of the head and the limbs (Cools et al , 1970, 1971, see 3 1 and 3 2)

In view of the mentioned considerations the present study was designed to examine in more detail the temporal patterning of the induced limb movements

3 3 3 METHODS

A detailed account of the experimental technique has already been published (Cools et al , 1970, see 3 1 2) Briefly, double barrelled cannulas were stereotaxically implanted into the brain of male cats Upon complete recovery from the operation, small quantities of drug solutions (10 0 µl) were injected through the injection needle which extended into the brain tissue 2 mm below the tip of the embedded cannulas Since it has been shown that DA application is "ineffective" in all caudate areas except from the caput caudati rostromedialis (Cools et al , 1970, see 3 1), brain site co-ordinates for placements discussed in this paper included this area (A = 14-16, L = 4-6 and H = 14-16) and the caput caudati anteroventralis (A = 17-19, L = 3-5 and H = 13-15) which was used as a control area (fig 3)

The following substances were injected saline (control), L-3,4-dihydroxyphenylalanine-HCl (L-DOPA), dopamine-HCl (DA), 3-methoxytyramine-HCl, noradrenaline-HCl (NA), 3,4-dihydroxyphenylacetic acid (DOPAC) and dexamphetamine-H_2SO_4, all drugs were dissolved in saline and adjusted to pH 4-5 In additional experiments pretreatment with the tyrosine hydroxylase inhibitor, α-methyl-para-tyrosine (methylester-HCl of DL-α-methyl-para-tyrosine α-MT) was given in order to test the specificity of the induced effects, 20 min prior to the application of DA or related compounds 20 0 µg α-MT was injected locally The temporal patterning of the limbs was recorded during a period of 45 min divided into nine time-blocks, 5 min each three before and six after the injection In each experiment six animals (12 injection-loci) were used

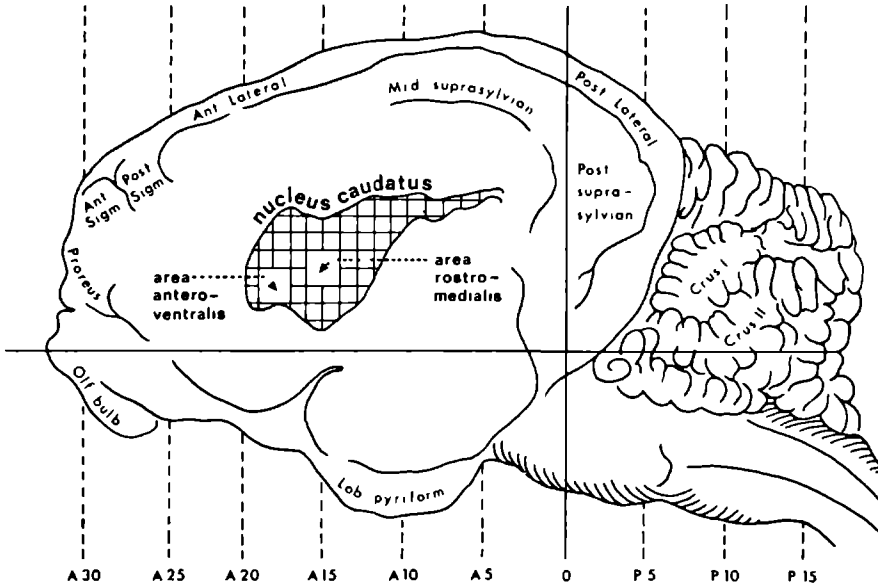

fig 3 Schematic diagram of the cat brain midsagittal projection of the caput nuclei caudati

3 3 4 RESULTS

In general, the abnormal limb movements following an injection of 10 0 ug DA into the caput caudati rostromedialis could be divided into two groups non-patterned movements involving the distal part of the limb and non-patterned movements involving the entire limb

3 3 4 1 Non-patterned movements involving the distal part of the limb

When the animal was standing, sitting or lying on its side, these movements began slowly the limb was lifted from the floor for a couple of seconds and the paw and toes underwent alternating hyperextension and flexion movements The alternating rhythmic ventriflexions and dorsiflexions were slow patterns rather than isolated acts and occurred either at rest or in the course of a voluntary action, in the last case the animal stopped the performance of the voluntary action when the movements appeared On many occasions the appearance was accompanied by piloerection and curling of the tail It occurred independently of the ongoing activity of the animal and the animal itself had no visual interest in the induced patterning of its limb The activity was restricted

to the forelimb contralateral to the injection-site in the case of L-DOPA (10 0 µg) and 3-methoxytyramine (10 0 and 80 0 µg), in the case of a higher dose of L-DOPA (25 0 µg), it was mainly restricted to the non-injected side Furthermore, it was alternating from one forelimb to the other in the case of dexamphetamine (10 0 and 144 0 µg) and high doses of DA (80 0 µg)

3 3 4 2 Non-patterned movements involving the entire limb

These movements occurred only when the animal was standing or sitting Usually, they followed up or interrupted the above-mentioned movements The limb was lifted from the floor and it showed rapid, jerky, shaking-off movements involving the entire limb, these movements were repeated several times in an irregular way The series of abrupt, gross irregular movements was violent and choreiform in nature Apart from the fact that the animal had continuous visual interest in these movements, it began to clean and to lick the affected limb in an intense way, when the movements disappeared These choreiform movements were induced not only in the forelimb, but also in the hindlimb

table 5

Quantitative aspects of the athetoid and choreiform episodes in the cat after microinjections into the rostromedial part of the caput caudati * Numbers of episodes are scored as follows 0 = none, 1 = 1-3, 2= 4-6, 3 ⩾ 7

COMPOUND	Dose (µg/10 µl)	post-injection time intervals (min) 0-1	2-3	4-5	6-10	11-15
L-DOPA	10 0	0	1	1	0	0
	25 0	0	2	1	1	0
Dopamine	10 0	0	1	0	0	0
	80 0	0	2	1	1	0
DOPAC	10 0	0	0	0	0	0
	80 0	0	0	0	0	0
3-Methoxytyramine	10 0	0	1	1	0	0
	80 0	0	1	1	0	0
Noradrenaline	10 0	0	0	0	0	0
	80 0	0	0	0	0	0
Dexamphetamine	10 0	0	3	2	1	1
	144 0	0	3	2	1	1
NaCl (saline)	90 0	0	0	0	0	0

* The number of gross limb movements are varying from 1-10 per episode

In general, both kinds of movements appeared as episodes of which the frequency had a maximum in the middle of the first 5 min period following the injection; occasionally the choreiform movements were also present in the second and third 5 min period. The irregular movements of the limbs were always elicited by small doses (10.0 μg) of L-DOPA, DA, 3-methoxytyramine and dexamphetamine administered into the caput caudati rostromedialis. No limb movements were noted when saline (control), NA or DOPAC were applied (table 5); even high doses (80.0 μg) were ineffective. The most effective dose of L-DOPA and DA was 25.0 μg and 80 0 μg, respectively; 3-methoxytyramine was equally effective in spite of the dose (10 0 μg-80.0 μg). The effect of dexamphetamine was markedly increased in comparison with the maximum effect of DA; not only the intensity of the movements was increased, but also the episode itself was prolonged. However, extending the dose range from 10.0 μg to 144.0 μg yielded no further increase in effect.
Of the brain areas sampled, the movements were always elicited from the caput caudati rostromedialis, although the intensity and frequency varied considerably between animals. Animals in which the compounds were administered into the caput caudati anteroventralis sometimes exhibited these movements; if present, the latency of their appearance was increased from 2-3 min to 20-24 min and the frequency was strongly decreased. When α-MT was given 20 min prior to the effective compounds, the limb movements induced by low doses (10.0 μg) of L-DOPA, DA, 3-methoxytyramine and dexamphetamine were totally suppressed. High doses (80.0 μg) of only L-DOPA, DA and dexamphetamine surmounted the inhibition and induced the originally elicited irregular patterns; in contrast, 3-methoxytyramine remained ineffective in spite of high doses (80.0 μg).

3.3.5. DISCUSSION

The non-patterned movements involving the distal part of the limb and the non-patterned movements involving the entire limb must be described as athetoid and choreiform movements, respectively, in reference to the terminology used by Liles and Davis in their lesion study (1969a). In fact, no distinguishable differences could be found between our observations and their detailed descriptions. However, small differences were noted with respect to the side of occurrence: in the lesion study the athetoid movements normally appeared in both forelimbs, while they occasionally occurred in the forelimb contralateral to the lesion site; in our study these movements were always restricted to the forelimb contralateral to the injection site in the case of low doses of L-DOPA, DA and 3-methoxytyramine, while they were alternating from one forelimb to the other in the case of dexamphetamine and high doses of L-DOPA and of DA. Although 3-methoxytyramine appeared to be just as effective as DA, the non-

competitive inhibition of its effect by the DA synthesis inhibitor, α-MT, and the ineffectiveness of the other DA metabolites, DOPAC and NA, indicate that the abnormal patternings of the limb movements must be regarded as "dopamine-specific' effects, the effectiveness of high doses of only L-DOPA, DA and dexamphetamine following inhibition of the DA synthesis strengthens this assumption

The observation that DA and related compounds were only effective in the caput caudati rostromedialis is in agreement with our previously reported conclusion that the DA-sensitive sites are restricted to the rostromedial area (Cools et al , 1970, see 3 1)

In regard to the data of Liles and Davis (1969a) the conclusion can be drawn that two clearly distinct areas of the caudate nucleus are involved in these symptoms the rostromedial area following DA application and the anteroventral area following electrolytic lesion Since neither DA application into the anteroventral area nor lesion in the rostromedial area led to the mentioned hyperkinesias, these areas must have different functions It has been shown that the head of the caudate nucleus represents localized functional regions the inhibiting anteroventral region and the facilitating rostromedial region * (Liles et al , 1969b) In a previous report we have found some indications that DA in the rostromedial area might induce activation of inhibiting neurons (Cools, 1971, see 3 2) In view of these findings it is reasonable to suggest that the DA-sensitive sites which are restricted to the caput caudati rostromedialis belong to very small inhibiting neurons which project to the caput caudati anteroventralis activation of these interneurons or lesions of the cell bodies controlled by these neurons results in the same effect Although the nature of these interneurons is so far unknown, extremely small caliber neurons have been observed previously in the caput caudati of cats (Adinolfi, 1967)

The most important result, however, is the discovery that the choreo-athetoid hyperkinesias are elicited from the caudate nucleus in which DA normally occurs in terminal structures of nerve-endings (Fuxe, 1965) Thus, activation or overactivation of normally DA-sensitive sites leads to choreo-athetoid hyperkinesias

In view of these data, the hypothesis can be put forward that normally DA-sensitive sites (of the caudate nucleus) are also involved as the target sites of choreo-athetoid movements observed in human beings This working hypothesis is formulated on the basis of three adequately proven facts (a) choreo-athetoid movements are induced in a significant number of parkinsonian patients after long-term L-DOPA treatment (see 3 3 2), (b) L-DOPA orally administered in animals induces a highly specific accumulation of DA in the caudate nucleus (Pletscher, 1969), (c) L-DOPA or DA locally applied into the

* Rostromedial area corresponds partially to the posterodorsal area of Liles and Davis (1969a, b)

caudate nucleus of cats induces movement disorders which are strikingly similar to the behaviour neurologists have seen in patients treated with L-DOPA and in patients with Huntington's chorea

This may have the implication that the enthusiasm for L-DOPA treatment must be tempered there is no evidence that the intracaudate DA-level involved in the therapeutic effects is different from the intracaudate DA-level involved in the side-effects as mentioned, on reaching therapeutic L-DOPA-levels the choreo-athetoid hyperkinesias appear in a large number of parkinsonians (Papavasiliou et al, 1969)

On the other hand, the continuing controversy of L-DOPA efficacy may also be explained on the basis of the neostriatal acetylcholine-dopamine imbalance, the importance of which has been stressed from results of several animal studies (Arnfred et al, 1968, Connor, 1966, Scheel-Kruger, 1970) Although it is generally accepted that the imbalance in the normal relationship between DA and acetylcholine in parkinsonians results from the primary involvement of a deficient DA-input in the neostriatum (Hornykiewicz, 1966, Klawans, 1968), the antiparkinson activity of anticholinergic drugs (Feldberg, 1945, Klawans, 1968), the parkinson-reinforcing activity of cholinesterase inhibitors (Duvoisin, 1967) and the ineffectiveness of L-DOPA in some parkinsonians (Klawans et al, 1970b) do not exclude the possibility that the imbalance in some patients may result from a primary involvement of cholinergic systems in other words, an imbalance resulting from an overactivity of the caudato-nigral cholinergic system rather than from a deficiency in the nigro-caudate DA system It is reasonable to suggest that L-DOPA treatment of these patients always results in an overactivation of the DA-sensitive sites and, thus, in choreo-athetoid hyperkinesias However, it remains to be investigated whether this occurs in the patients whose condition is not alleviated by L-DOPA Summarizing, these considerations indicate that further experience will be required before L-DOPA can be accepted as the most successful drug in the treatment of Parkinson's disease

As a final remark, the described movements induced by locally applied L-DOPA or DA support the hypothesis that choreiform movements observed in Huntington's chorea are due to an overactivation of the DA-sensitive sites in the caudate nucleus (Klawans, 1970a) According to this hypothesis inhibition of the overactivation must consequently lead to the suppression of these movements, this indicates that inhibition of the DA activity may have some therapeutic value in Huntington's chorea Indeed, Papavasiliou et al (1969) reported that α-methyl-DOPA, a depletor of catecholamines, induced a significant diminution of these movements On the other hand, cholinesterase inhibitors also induce a reduction in the choreiform movements (Aquilonius et al, 1971) This again suggests that motor disorders of the basal ganglia result from the difference in the absolute activities of DA and acetylcholine rather than from the absolute activity of only one of them

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3 4 THE INTERDEPENDENCY OF ELECTRICALLY EVOKED EFFECTS AND DOPAMINE-INDUCED BEHAVIOUR: THE FACILITATORY ROLE OF DOPAMINE

3 4 1 ABSTRACT

Behavioural effects of electrical stimulation of the rostromedial part of the caput caudati were studied in freely moving cats in chronic experiments These electrically evoked effects were also studied in animals locally pretreated with dexamphetamine, apomorphine, dopamine (DA), 3-methoxytyramine, noradrenaline (NA), serotonin (5-HT), haloperidol, α-methyl-para-tyrosine (α-MT) and procaine. Our data show that electrical stimulation of the rostromedial part of the caput caudati results in behavioural responses similar to those evoked by DA application into this area, and that these responses are inhibited by blockade of the caudate DA system on the one hand, and facilitated by activation of the caudate DA system on the other hand. The importance of these data is discussed in view of the hypothesis that DA released from the ascending nigro-caudate pathways activates small inhibiting interneurons connecting the rostromedial part of the caput caudati with the anteroventral part of the caput caudati.

3 4 2 INTRODUCTION

Recently, Cools et al (1970, see 3 1) have demonstrated that dopamine (DA) unilaterally introduced into the caudate nucleus of cats resulted in a DA-specific syndrome, mainly marked by contralateral movements of the head and abnormal movements of the contralateral forelimb Evidence from a variety of sources indicates a neurotransmitter role for DA in this part of the brain (Hornykiewicz, 1966). According to the results of Bloom et al. (1965), Connor (1970), Herz et al. (1968) and Feltz (1970), inhibition is the most consistent effect of iontophoretically applied DA on the activity of single neurons in the brain; Herz et al (1966) and van Rossum et al (1966) therefore suggested that DA might act as a postsynaptic inhibitor. Accordingly, it seems reasonable to assume that inhibition of the neuronal activity induced by DA might underly the DA-specific syndrome. However, we have obtained evidence (Cools, 1971; see 3 2.) that suppression of the neuronal activity induced by procaine application into the same part of the brain did not result in the DA effects, in fact, it resulted in effects diametrically opposite to those elicited by DA : particularly, ipsilateral movements of the head and abnormal movements of the ipsilateral forelimb. The same holds true for the effects induced by lesions in the caudate nucleus as shown by Gijbels (1965) These data suggest that activation rather than inhibition of the neuronal activity is involved in the process of eliciting the DA syndrome

As electrical stimulation with carefully controlled stimulus variables induces effects due to activation of either facilitating or inhibiting neuronal elements, it is of great interest to consider the effects elicited by this technique
A review of this literature (Akert et al , 1951, Forman et al , 1957, Laursen, 1963, Rozhanskii et al , 1957, Stevens et al , 1961) suggests that at least some responses induced by high frequency stimulation of the caudate nucleus resemble the above-mentioned DA responses In view of this similarity, it is attractive to postulate that both electrical stimulation and DA stimulation evoke these responses by means of one common mechanism of action If so, then the evidence for an activating action of DA in this part of the brain would be greatly strengthened
These considerations have prompted us to investigate whether electrical stimulation of the DA-sensitive area within the caudate nucleus of cats results in DA-like responses, and whether these effects are dependent on the presence of DA in this area The data reported here show that electrical stimulation of the DA-sensitive area results in responses similar to those evoked by DA, and that these responses are facilitated by activation of the caudate DA system on the one hand, and inhibited by blockade of the caudate DA system on the other hand

3 4 3 METHODS

Subjects 29 male cats, ranging in weight from 2 5 to 3 5 kg, were used in these experiments All animals were maintained on an ad libitum feeding schedule throughout the experiments The temperature (22° C), day/night periodicity and light intensity were standardized
Surgical procedures Firstly, double barrelled, stainless steel cannulas were implanted stereotaxically into both the right and left caudate nucleus as described in previous publications (Cools et al , 1970, see 3 1 3) (co-ordinates were chosen according to the atlas of Jasper et al (1954) A = 14-15, L = 4-6, H = 14-17) Secondly, insulated stainless steel electrodes, 0 35 mm in diameter, impedance of 20 kΩ to 30 kΩ and bared about one mm from the tip,were implanted a rostal-caudal and a medial-lateral couple of electrodes were placed around each injection-locus, following Laursen (1963), the tips were placed two mm apart After the implanted electrodes had been connected to a receptacle (a slightly modified Amphenol connector, type 222-3-2-N, Rodelco), the unit was surrounded by a teflon ring and mounted on the skull just above the frontal sinus by means of galvanized screws The general procedure employed did not differ from that employed by Reeves et al (1968)
Experimental procedures The experiments were performed in a 90 x 90 x 40 cm cage having a clear plexiglass front for observation and tape-recording In general, the behavioural effects were recorded by a closed TV circuit, the

tapes provided objective and continuous records which were analysed with the aid of a standardized list of items (table 6) In the electrical stimulation studies, the electrodes were stimulated with bipolar stimuli consisting of 30 sec trains of rectangular biphasic pulses of 0 5 msec duration, the intensity varied from 100 uA to 1000 μA, most often from 300 uA to 400 μA In the chemical stimulation studies, small quantities (10 0 μl) of the following compounds were given unilaterally through a needle which extended into the brain tissue two mm below the tip of the embedded cannulas saline (NaCl 90 0 ug), dopamine-HCl (DA 10 0 ug), 3-methoxytyramine-HCl (10 0 ug), noradrenaline-HCl (NA 10 0 μg), dexamphetamine-H_2SO_4 (i e a DA releasing agent (Hanson, 1967) 10 0 μg), apomorphine-HCl (a putative DA-receptor agonist (Ernst et al , 1966) 0 6 μg), haloperidol (a putative DA-receptor antagonist (Cools, 1971, van Rossum et al , 1964, see 3 2) 25 0 μg), methylester-HCl of DL-α-methyl-para-tyrosine (αMT, a potent inhibitor of DA synthesis (Spector et al , 1965) 20 0 μg), 5-hydroxytryptamine creatinine sulphate (5-HT 10 0 μg) and procaine (10 0 μg) The compounds were dissolved in saline and adjusted to pH 4-5, apart from haloperidol which was given as Serenase® (Janssen Pharmaceutica, Belgium) In preliminary experiments, it was found that the above-mentioned pH had no influence on the effects induced, diffusion was checked by means of autoradiographic methods an injection of DA (10 0 μg/10 0 μl) resulted in a diffusion area of about two square mm after a period of 15 min All substances were injected in at least 7 injection-loci in different animals The maximum number of injections per cannula was restricted to eight

After habituation of the cat to the cage and connection cable during two sessions of one hour each, the experiments were initiated In the first group of experiments, electrical stimulation was applied to investigate the mutual dependency of frequency and intensity with respect to evoking contralateral motor responses (3 animals, 12 electrode-couples) In the second group of experiments, the motor responses elicited by electrical stimulation were analysed in detail (21 animals, 66 electrode-couples) The recording period of 150 sec was divided into a pre-stimulation period (60 sec), a stimulation-on period (30 sec) and a post-stimulation period (60 sec), during these periods the presence or absence of each item was registered, while special symbols were listed for the items 8, 10, 13, 18, 19 and 34 (table 6) As initial postures of the cats determined the elicited motor responses to a large degree, stimuli were only applied to animals which were lying in a normal posture flexed fore- and hindlimbs, normal neck tension and open eyes, no stimuli were applied to animals which were moving or sleeping In the third group of experiments, stimuli effective in evoking motor responses were repeated at different time-intervals (2, 4, 6, 8, 10 and 12 min) in order to study the refractory phase of the stimulation, knowledge about the refractory phase was necessary in view of the experiments mentioned below The effects were determined in five cats (20 electrode-couples) In the final group of experiments, the influence of

table 6

Ethogram of the cat the presence or absence of the listed items was recorded during each minute of the 45 min observation period, special symbols were listed for the items 8, 10, 13, 18, 19 and 34*.

"Dynamic Units"	"Static Units"	"Sense Units"	"Specific Units"	
1 Lying	8 Head movement	14 Miosis	21 Chewing	30 Mouth-opening
2 Sitting	9 Neck tension	15 Mydriasis	22 Licking	31 Tongue extrusion
3 Standing	10 Tail movement	16 Ptosis	23 Swallowing	32 Piloerection
4 Walking	11 Forelimb extension	17 Nictitating membrane	24 Sniffing	33 Convulsion
5 Moving	12 Hindlimb extension	18 Eye-opening	25 Miaowing	34 Respiration rate
6 Exploring	13 Posture	19 Ear-movement	26 Gasping	35 Urination
7 Springing		20 Clawing	27 Staring	36 Defecating
			28 Swinging	37 Cleaning
			29 Trampling	38 Crouching
				39 Backward locomotion

* "Response Units" are the items 1-39, recorded during a noise stimulus presented at the end of each time-block (5 min)

chemical stimulation on electrical stimulation was investigated (14 animals, 56 electrode-couples and 28 injection-loci)
Firstly, the effectiveness of locally applied substances was determined according to previously described methods (Cools et al , 1970, see 3 1 3) The appearance of the drug-specific syndromes which have been extensively described previously (Cools et al , 1970, Cools, 1971, 1972a, see 3 1 , 3 2 and 3 3) were used as test-parameters
Secondly, subthreshold and threshold intensities were given to animals locally pretreated with the above-mentioned substances at 10 min and 20 min after the injection, in the case of α-MT, they were given at 30 min and 40 min after the injection as well Control stimulation was delivered 10 min before the injection Both threshold and subthreshold values were determined in four sessions during two successive days, the subthreshold intensity was determined by testing an intensity of 50, 100 or 150 μA lower than the threshold intensity effective in evoking the contralateral movements, and selected according to the following criteria absence of the characteristic movements, and presence of only after-stimulus effects The criteria for determining the influence of the substances on the electrical stimulation effects are described in the results section After finishing the stimulation experiments, electrolytic lesions of the stimulation points were made by passing an anodal DC current of 1 0 mA for 15 sec
Histological procedure After completion of the experiments, the cats were sacrificed under anesthesia i e perfused through the heart with saline and subsequently with 10% formaldehyde solution The brains were removed and fixed in 4% formaldehyde solution For the precise identification of the loci, 40 μ frontal sections of the brain were made and stained with acidified 0 25% cresyl violet The location was determined by reference to the atlas of Jasper et al (1954)

3 4 4 RESULTS

3 4 4 1 Electrical stimulation

A Mutual dependency of frequency and intensity
The criterion for selection of the motor responses was chosen in accordance with the investigations of Forman et al (1957), Laursen (1963) and Stevens et al (1961) contralateral turning of the head As shown in table 7, only frequencies of 20/sec and 30/sec were effective in meeting the mentioned criterion for 75% of the tested couples using an intensity of 300 μA to 400 μA, lower intensities did not elicit any motor responses apart from a long-term hypokinesia Associated effects such as salivation, piloerection, mydriasis, crouching and plaintive crying were most often noted in the case of stimulation at 30/sec Therefore, stimulation at 20/sec was used in the experiments mention-

table 7

The number of intracaudate stimulation points (n = 12) effective in evoking contralateral head movements in freely moving cats in relation to the frequency and intensity of the stimulus

μA	Hz 2/sec	4/sec	10/sec	20/sec	30/sec
100	0	0	0	0	2
200	0	0	0	4	4
300	0	2	0	9	9 (5*)
400	0	2	0	9	12 (6*)
500	0	0	4	12	11 (9*)
600	0	2	2	11	12 (9*)
700	0	2	—	—	—
800	0	3*	—		
900	0	—	—	pulse 0 5 msec	
1000	2*	—	—	train 30 sec	

* Additional side-effects, see also text

ed below All sites of the electrode-tips (24) were located within the shaded areas of figs 4 and 5

B Motor responses

a Stimulation of 41 couples (62 1%) resulted in a so-called *rhythmic* "contralateral" syndrome, marked by rhythmic contralateral turning of the head, choreo-athetosis of the contralateral forelimb and associated effects (type 1) Normally, these animals maintained the lying posture during the whole stimulation period (80 5%) However, some animals (7 3%) stood up, and then, sat down or kept the standing posture without walking around, 9 3% of the *animals started to circle contralaterally Exploring and springing were not* observed, moving, i e falling down on the stimulated side, was observed once After a latency varying from 3-16 sec, rhythmic movements of the head towards the non-stimulated side appeared, the neck tension remained normal during these activities Within a period of 10-20 sec contractions of the contralateral facial muscles and turning of the eye-balls appeared in 61 0% of the tested animals Alternating hyperextension and flexion movements of the contralateral fore-paw and toes (athetoid in nature) and rapid, jerky, shaking-off movements involving the entire forelimb (choreiform in nature) appeared within 16-25 sec Pupillary dilatation was noted after a latency of 18-30 sec in 14 6% of the tested cases, ptosis, contractions of the contralateral nictitating

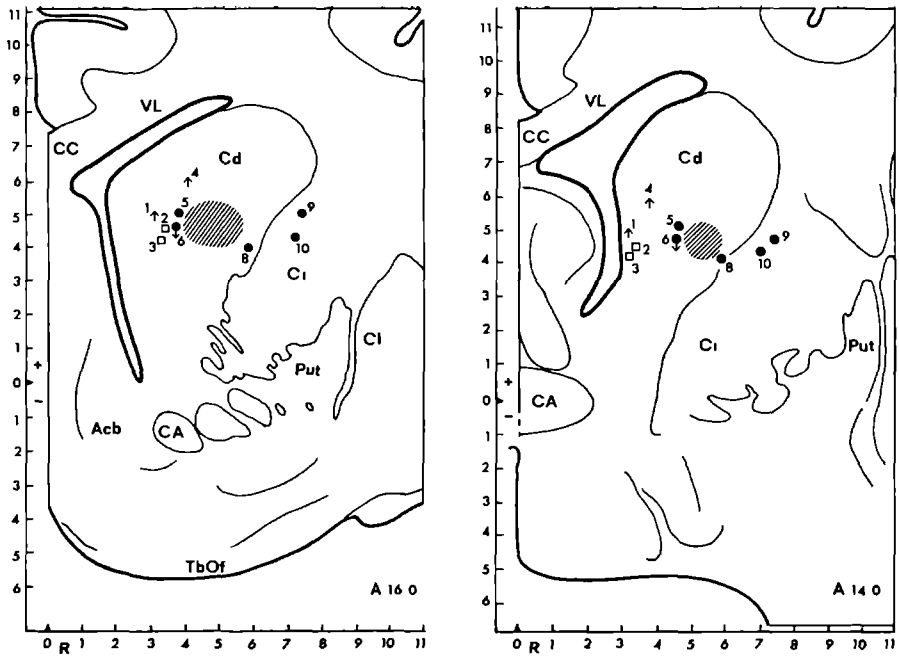

fig 4 Semi-diagrammatic outlines of two anterior frontal planes of the basal ganglia (A = 14 0 and 16 0) showing the sites of stimulation points of medial-lateral electrode-couples producing the rhythmic "contralateral" syndrome (●), the non-rhythmic "contralateral" syndrome (●), akinesia (□) and the "cleaning" syndrome (↟) Sites of electrodes in each electrode-couple have corresponding figures The shaded areas cover the sites of 15 electrode-couples producing the "contralateral" syndrome For abbreviations. see appendix

membrane and fluttering of both ears were noted in 7 3%, 7 3% and 19 5% of the tested animals respectively None of the remaining items mentioned in table 6 apart from cleaning (26 8%) were more than incidental observations

b Stimulation of 17 couples (25 8%) resulted in a so-called *non-rhythmic* "contralateral" syndrome, marked by non-rhythmic contralateral movements of the head (type 2), sometimes these symptoms were accompanied by flexions of the contralateral forelimb (35 3%) In all cases, the latency of the turning effect was increased in comparison with the latency of this effect in the above-mentioned syndrome No other effects were observed

c Stimulation of two couples (3 0%) resulted in a syndrome, marked by cleaning activities (the so-called "cleaning" syndrome type 3), intensive licking and cleaning activities, especially of the ipsilateral hindlimb, started without any delay and lasted longer than the stimulation period itself

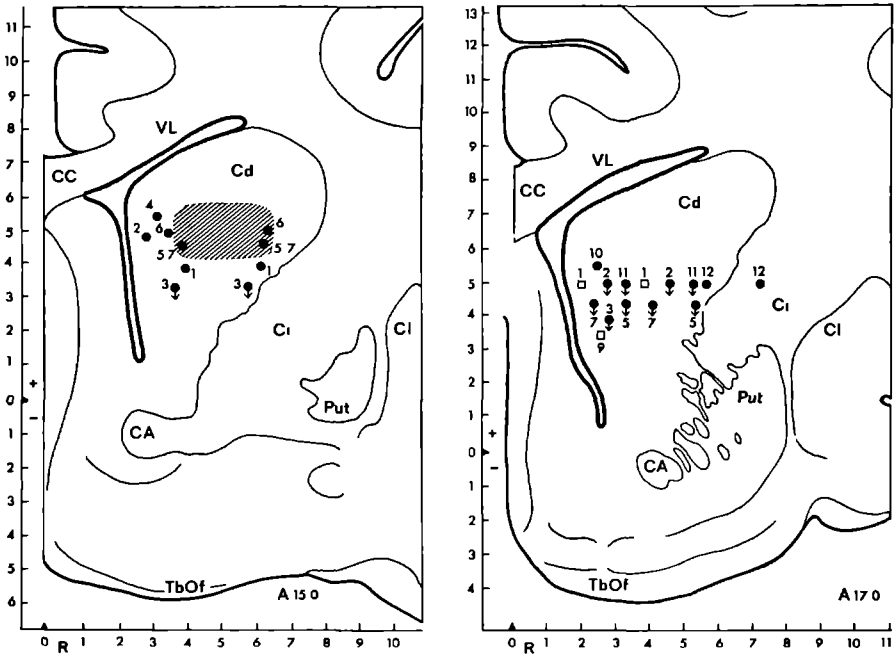

fig 5 Semi-diagrammatic outlines of two anterior frontal planes of the basal ganglia (A = 15 0 and 17 0) showing the sites of stimulation points of rostral-caudal electrode-couples producing the syndroms mentioned in fig 4 The shaded area covers the sites of 17 electrode-couples producing the rhythmic ' contralateral" syndrome

d Stimulation of two other couples (3 0%) resulted in rhythmic ipsilateral turning of the head accompanied by choreo-athetosis of one forelimb (the so-called "ipsilateral" syndrome type 4)

e Finally, stimulation of the four remaining loci (6 1%) resulted in a hypokinetic syndrome (type 5) the animals lay without any spontaneous movement, lost their neck tension and failed to respond to acoustic stimuli for a long time

In general, animals showing motor responses during the stimulation period itself also showed after-stimulus effects In the case of types 1 and 2, these effects consisted of a short-term fixation of the head in the contralateral direction followed by turning towards the stimulated side, activities such as tongue extrusion, licking and miaowing appeared 3-15 sec after the stimulus stopped All above-mentioned types persisted unchanged in four sessions during two successive days

The sites of the electrode-tips are schematically shown in figs 4, 5 and 6 Apparently, the stimulation points effective in eliciting different syndromes are scattered around within the same area However, it is interesting to mention that those points which were effective in producing the hypokinetic syndrome were found in the vicinity of the lateral ventricle (fig 4 2 and 3, fig 5 1 and 9), while those points which were effective in producing the "ipsilateral" syndrome were found in the most rostral part of the tested area (fig 6 14 and 18) It is remarkable that those couples found within the internal capsule were also effective in producing the non-rhythmic "contralateral" sydrome (fig 4 9 and 10)

C Refractory phase

Re-stimulation within 6 min of initially effective points was "ineffective" in 60 0% of the 20 tested couples these animals showed a loss of spontaneous movements and failed to respond to sensory stimuli for a long period In the case of a time-delay of 8 min between the stimuli, the initially evoked responses persisted in 90 0% of the tested couples, in the case of a time-delay of 10 min or more, the motor responses persisted unchanged in all tested couples, even during six successive sessions All electrode-tips of the 20 tested couples were located within the shaded area of figs 4 and 5

3 4 4 2 Chemical stimulation

In view of the fact that the effects induced by local application of the drugs mentioned in the methods were described earlier (see 3 1), only a brief survey is given here

Unilateral injections of DA (10 0 μg), dexamphetamine (10 0 μg), apomorphine (0 6 μg) and 3-methoxytyramine (10 0 μg) respectively resulted in a syndrome marked by a reduction of the locomotor activity, contralateral turning of the head, choreo-athetosis of the contralateral forelimb, contractions of the contralateral facial muscles, contralateral turning of the eye-balls, contralateral ptosis, miosis and alternating periods of rest and activity (cf type 1 elicited by electrical stimulation)

Unilateral injections of procaine (10 0 μg) and haloperidol (25 0 μg) resulted in a syndrome marked by ipsilateral turning of the head and choreo-athetosis of the ipsilateral forelimb (cf type 4 elicited by electrical stimulation)

In general, these symptoms appeared at the end of the first five minutes apart from the choreo-athetosis which appeared in the middle of this period, they had nearly a constant frequency during the next period of five minutes, and disappeared within the following period of five minutes

α-MT (20 0 μg) resulted in ipsilateral turning of the head, and movements of the ipsilateral forelimb after a latency of about 25 min

Apart from an increased licking and cleaning activity after a latency of about

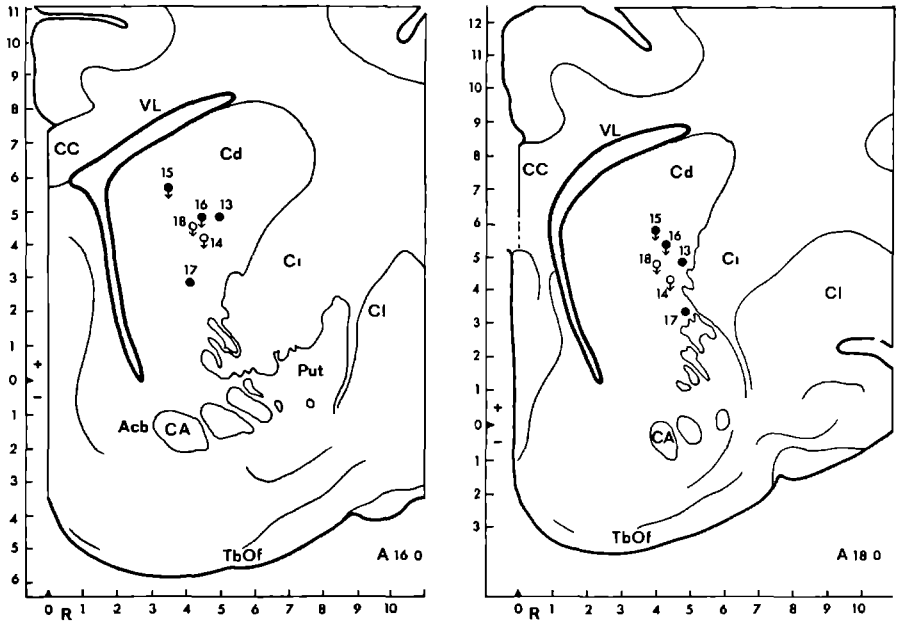

fig 6 Semi-diagrammatic outlines of two anterior frontal planes of the basal ganglia (A = 16 0 and 18 0) showing the sites of stimulation points of rostral-caudal electrode-couples producing several syndromes including the "ipsilateral" syndrome (open symbol), see also fig 4

10 min, 5-HT (10 0 μg) had no effect at all; injections of NA (10 0 μg) and saline were also ineffective.

Application of DA into 29 of the 33 injection-loci resulted in the above-mentioned effects Although the frequency and intensity of the induced symptoms varied strongly per animal, the effects persisted unchanged in two sessions during two weeks. The effects elicited from three loci were inconsistent with respect to repetitive application, while no effects were elicited from one locus. The other drugs were tested separately in at least 7 injection-loci, and were found to be effective in all animals in which DA resulted in the "dopamine-specific" syndrome. All sites of the needle-tips were located within the shaded areas of figs 4 and 5

3 4.4 3. The role of DA in electrical stimulation

Animals in which both electrical and chemical stimulation produced the "contralateral" syndrome were used in the chemical-electrical stimulation study (14 animals; 56 electrode-couples and 28 injection-loci). The criteria for

determining the influence of drugs upon electrical stimulation effects were as follows

(Aa) appearance of rhythmic contralateral head movements and choreo-athetosis of the contralateral forelimb during *subthreshold* stimulation of locally pretreated animals in which *threshold* stimulation resulted in type 1 (facilitation), (Ab) appearance of non-rhythmic contralateral head movements during *subthreshold* stimulation of locally pretreated animals in which *threshold* stimulation resulted in type 2 (facilitation), (B) no reactions during *threshold* stimulation of locally pretreated animals in which *threshold* stimulation resulted in type 1 or 2 (inhibition), and (C) no change in the symptoms during *threshold* stimulation of locally pretreated animals in which *threshold* stimulation resulted in type 1 or 2 (ineffectiveness)

Firstly, DA injections (10 0 ug, n = 31) resulted in the so-called facilitation of the subthreshold stimulation effects in 83 9% of the tested cases In fact, not only head movements and choreo-athetosis, but also cleaning and licking activities appeared in a great number of animals, regardless of the initially evoked types Moreover, subthreshold stimulation of some animals which initially showed type 2, resulted in the appearance of type 1 (10 7%), apparently, both types were closely related to each other In additional tests, an increase in the symptoms with respect to their intensity was observed during threshold stimulation of the pretreated animals, in view of the lack of reliable measures in this respect, no data were analysed in detail Stimulation effects of the remaining loci (16 1%) were uninfluenced by the application of DA

Secondly, 3-methoxytyramine (10 0 µg), dexamphetamine (10 0 µg) and apomorphine (0 6 ug) injections (n = 7/substance) also induced facilitation, in contrast to animals pretreated with 3-methoxytyramine, animals pretreated with dexamphetamine or apomorphine showed associated effects such as cleaning and licking

Thirdly, application of 5-HT (10 0 µg, n = 8), NA (10 0 µg, n = 7), and saline (n = 7) did not have any effect upon the symptoms elicited by threshold or subthreshold stimulation (ineffectiveness)

Fourthly, haloperidol (25 0 µg, n = 8) and procaine (10 0 µg, n = 7) inhibited the threshold stimulation effects in all experiments except for one (inhibition), in this test, the haloperidol injection itself failed to induce the expected behavioural change

The above-mentioned influences of the drug pretreatment upon the electrical stimulation were determined at 10 min to 12 min after the injection The effects of re-stimulation at 20 min to 22 min after the injection were less influenced by DA, dexamphetamine, apomorphine, and even uninfluenced by 3-methoxytyramine In contrast, the influence of haloperidol persisted unchanged in 71 4% of the tested animals during re-stimulation

Finally, α-MT pretreatment (20 0 µg, n = 6) resulted in a time-dependent inhibition of the symptoms elicited by threshold stimulation (table 8) Lesioning

table 8

The time-dependent effects of intracaudate administered α-MT (20 0 ug) upon electrical stimulation effects evoked from the rostromedial part of the caput caudati in cats.

Cat no	Behavioural effects of electrical stimulation at pre- and post-injection time-intervals (min).					
	-10	0	10	20	30	40
1	bcd		ad	—	bd	bcd
2	bcd		ad	—	bd	bcd
3	bcd		ad	—	ad	bcd
4	bcd		a	—	bd	bcd
5	bcd		ad	—	bcd	bcd
6	bcd		ad	a	bcd	bcd

a· subliminal effect
b: contralateral turning of the head
c choreo-athetosis
d· after-stimulus effects

of the points resulted in a short-term contralateral turning effect immediately followed by strong ipsilateral head turning accompanied by wild, uncontrolled movements of the ipsilateral forelimb, mydriasis, salivation and falling down on the lesioned side; no behavioural abnormalities were observed during sessions one week after the lesion.

3 4 5 DISCUSSION

Intermediate frequency stimulation (20/sec) of the head of the caudate nucleus in cats is found to elicit several types of motor responses. The most important type occurring in 87.9% of the experiments is the so-called "contralateral" syndrome, mainly marked by contralateral movements of the head and abnormal movements of the contralateral forelimb, athetoid and choreiform in nature. It is well known that a great number of diverse motor responses varying from complete inhibition of movements to circling towards the non-stimulated side can be elicited from the caudate nucleus. In view of the different stimulus variables used, it is difficult to compare our data with those reported in the literature (Akert et al., 1951, Forman et al., 1957; Laursen, 1963; Rozhanskii et al , 1957, Stevens et al , 1961). However, there is a remarkable agreement with

those described by Akert et al (1951) He and his co-worker reported the following effects as a consequence of intracaudate stimulation in cats inactivation and raising of the overall threshold for external stimuli, ptosis, miosis, abnormal position of the limbs low respiration rate and motor effects on the non-stimulated side of the body Although they argued that the contralateral effects were the results of capsule stimulation as a consequence of irradiation, Laursen (1962, 1963) using electrical stimulation of both the caudate nucleus and the internal capsule has given evidence that the contralateral effects of the head are characteristic for intracaudate stimulation

It is worth mentioning that several symptoms of the syndrome reported here are described as independent symptoms induced by quite different stimulus variables for instance, contralateral turning of the head are described by Laursen (1963) as the consequence of high frcquency stimulation, while contractions of the facial muscles and narrowing of the palpebral fissures are described by Akert et al (1951) as the consequences of low frequency stimulation Since the symptoms reported here are highly reproducible and occur in a large number of the tested cases, these discrepancies probably reflect differences in experimental approaches

The most important finding, however, is the fact that the motor responses produced by electrical stimulation using carefully selected stimulus variables are strikingly similar to those evoked by local application of DA (10 0 µg) not only the same muscular groups are involved, but also the same type of movements are induced Although it is known that activation of totally different mechanisms may result in the elicitation of identical behavioural patterns, the following facts give evidence that only one mechanism of action appears to be involved in both manipulation techniques used in our experiments Firstly, the effective electrode-sites are found within the area to which the DA-sensitive sites are restricted as shown in our previous experiments (Cools et al , 1970, see 3 1) Secondly, as shown in the present experiments, inhibition of DA synthesis by means of α-MT or blockade of the DA-sensitive sites by means of haloperidol totally suppresses the electrical stimulation effects, moreover, increase in the DA content in this area or activation of the DA mechanism by means of dexamphetamine or apomorphine strongly facilitates these effects Finally, Riddell et al (1971) have given evidence that electrical stimulation results in an increased DA release in the caudate nucleus of cats In this context, it is noteworthy that the yield of DA release in the caudate nucleus following electrical stimulation of the substantia nigra or of the caudate nucleus is dependent on the frequency of the stimulation the highest total yield was obtained at 10-30/sec as reported by Von Voigtlander et al (1971), in our experiments, it was found that stimulation at 20/sec resulted in the best responses

In conclusion, caudate DA appears to be an indispensable link in the process of evoking the "contralateral" syndrome by means of electrical stimulation of

the DA-sensitive area In view of the large amount of literature referring to the DA nigro-neostriatal input, it is quite understandable that the ascending nigro-caudate pathway might be the source of the caudate DA release following electrical stimulation It is important to note that the caudate tissue recovers very slowly from the given stimulus the long refractory phase (about 10 min) may reflect the chemical reactions restoring the induced chemical changes In previous experiments (Cools, 1972a b, see 3 3), we have found that the contralateral effects induced by local application of rather low doses of DA (5 0-10 0 µg) into the caput caudati rostromedialis (CRM-area) were diametrically opposite to the ipsilateral effects elicited either by the application of higher doses of DA (25 0 µg) or by small electrolytic lesions in the same area these data suggested that the contralateral effects induced by low doses of DA might be due to activation rather than to suppression of the neuronal activity This is strongly supported by the fact that the ipsilateral effects induced by higher doses of DA are indiscernible from the ipsilateral effects produced by the application of procaine or the DA-receptor blocking agent haloperidol (Cools et al , 1970, Cools, 1971, see 3 1 and 3 2) On the other hand, the contralateral effects elicited by low doses of DA into the CRM-area were similar to those produced by lesions in the caput caudati anteroventralis (CAV-area) In addition, neither DA application into the CAV-area nor lesion in the CRM-area led to these effects

In view of these considerations, we have put forward the hypothesis that DA released from the ascending nigro-caudate pathways activates small inhibiting neurons connecting the CRM-area with the CAV-area (Cools, 1972b) The data presented here give evidence in support of the facilitatory nature of this process in the CRM-area Although a number of workers have reported that DA mainly inhibits the activity of single caudate neurons, Herz et al (1968) and others (Bloom et al , 1965, Connor, 1970, Feltz, 1970, York, 1967) have shown that DA also excites intracaudate neurons Some evidence in support of the DA nature of this excitatory input is also presented by Feltz (1971) who reported that haloperidol, a putative DA-receptor antagonist, inhibited the nigro-caudate excitatory input in some cases These results are in agreement with preliminary data derived from our experiments with the DA-receptors in the snail *Helix aspersa* some cells excited by DA were inhibited by haloperidol, while cells depressed by DA were unaffected by haloperidol (pers communication Gielen, W H J and van Rossum, J M , cf Woodruff, 1971) Our hypothesis fits in well with the hypothesis of Feltz et al (1972a), who assumed that the caudate interneurons receiving a direct excitatory input from the substantia nigra have an inhibitory output operating within the caudate nucleus itself On the other hand, Feltz et al (1972b) have recently shown that a pretreatment with 6-OH dopamine does not affect the monosynaptic excitatory input from the substantia nigra pointing to a possible involvement of non-dopaminergic fibres in the elicitation of the monosynaptic excitatory input

However, he and his co-worker (Feltz et al , 1972c) have also shown that DA iontophoretically applied to intracaudate cells restores total firing of cells when they are previously excessively depolarized by continuous application of glutamate It seems likely to assume that this DA mechanism is responsible for the behavioural effects observed in our experiments

However, since a correlation between nigral excitatory input and DA excitatory effects has until now only been established for the putamen as shown by York (1970), our hypothesis awaits confirmation from additional electrophysiological and neuropharmacolog.cal investigations.

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CHAPTER 4

INTRACAUDATE ADMINISTRATION OF SEROTONIN IN CATS

4.1. INTRACAUDATE SEROTONIN AND BEHAVIOUR OF CATS: THE SPECIFICITY AND ANTAGONISM OF THE SEROTONIN-INDUCED EFFECTS

4 1.1 ABSTRACT

In order to investigate the functional role of the anteroventral part of the caput caudati in cats, a behavioural study of locally applied 5-hydroxytryptamine (5-HT), dopamine (DA), dexamphetamine, carbachol, para-chlorophenylalanine (p-CPA), D-lysergic acid diethylamide (LSD-25) and procaine was undertaken. Behavioural parameters were employed to measure the action of drugs unilaterally injected through permanently implanted cannulas.
It could be demonstrated that small doses of 5-HT produced a consistent syndrome, marked by hyperkinesias, abortive and disjunctive self-directed activities, choreo-athetosis, "vacuum" activities and a "conditioning" effect. It was shown that this syndrome is 5-HT specific: pretreatment of the animals with p-CPA or LSD-25 blocked these effects in a competitive way. In contrast to DA, dexamphetamine produced a 5-HT-like syndrome which was blocked by p-CPA; pretreatment of the animals with haloperidol did not prevent the dexamphetamine syndrome. It is suggested that dexamphetamine also interferes with 5-HT in this part of the brain. The effects of LSD-25 and carbachol are discussed.

4 1 2. INTRODUCTION

It is currently believed that the basal ganglia regulate normal muscular activities by means of a complex system of facilitation and inhibition: disruption of this balance would lead to abnormal motor manifestations such as hyperkinesias, hypertonia, etc. (Monnier, 1970) The caudate nucleus, a large component of the basal ganglia, is loaded with putative neurotransmitters such as acetylcholine, dopamine (DA) and serotonin (5-HT) (Bertler et al., 1959; Bogdanski et al., 1956; Feldberg et al., 1948; Fuxe et al., 1966; Garattini et al., 1965; McLennan, 1966). During the last decade considerable information has become available regarding the association of intracaudate DA with specific behavioural patterns (Cools et al., 1970; Fog et al , 1967; Fuxe et al., 1970). Recently, it has been shown that DA locally introduced into the rostromedial

part of the caput caudati in cats induces a behavioural syndrome, marked by decrease in "specific units" such as licking and cleaning, by decrease in "dynamic units" such as walking and standing and by characteristic movements of the head and limbs (Cools et al , 1970, Cools, 1971, 1972, see 3 1 and 3 3) The non-patterned limb movements, athetoid and choreiform in nature, are particularly interesting in view of the fact that small lesions restricted to the anteroventral part of the caput caudati also result in the mentioned choreo-athetosis of the limbs (Liles et al , 1969a) Neither DA application into the anteroventral part of the caudate nucleus nor lesion of the rostromedial part of the caudate nucleus leads to this phenomenon (Cools, 1972, see 3 3) These data suggest a functional differentiation within the caudate nucleus Indeed, it has been reported that the head of the caudate nucleus in cats represents two localized functional regions the inhibiting anteroventral area and the facilitating rostromedial area (Liles et al , 1969b) Our interest was, therefore, strongly increased in the functional role of the so-called inhibiting anteroventral part of this nucleus

In the present study, the role of this part of the brain is investigated by means of selective chemical stimulation of structures, sensitive to putative neurotransmitters occurring in this part of the brain For this purpose, DA, 5-HT and the standard cholinomimetic drug, carbachol, are tested using intracaudate injections of small amounts, in view of the psychotomimetic action of dexamphetamine (Griffith et al , 1970) and its effect upon catecholamines (DA and noradrenaline (NA)) and indoleamines (e g 5-HT) (Fuxe et al , 1970, Schubert et al , 1970), a study of this compound is included In order to determine the specificity of 5-HT and dexamphetamine effects, these substances are also given to animals pretreated with (a) para-chlorophenylalanine (p-CPA), a potent inhibitor of 5-HT synthesis (Koe et al , 1966), with (b) haloperidol, a competitive antagonist of DA (Cools, 1971, see 3 2) and with (c) D-lysergic acid diethylamide (LSD-25), a possible 5-HT-receptor agonist (Aghajanian, 1972) Finally, reversible lesions are made by means of the local anesthetic procaine in order to analyse possible inhibitory aspects of the tested compounds

The results of the experiments reported here show that intracaudate 5-HT apparently functions as an important biochemical link in the complex process of eliciting, determining and adjusting the performance of some behavioural patterns

4 1 3 METHODS

The subjects were 17 male cats, ranging in weight from 2 5 to 3 5 kg All animals were maintained on an ad libitum feeding schedule throughout the experiments Double barrelled, stainless steel cannulas were stereotaxically

implanted into the right and left caudate nucleus, details of the procedure can be found elsewhere (Cools et al, 1970, see 3 1 3) After habituation of the cats to the cage during two sessions of one hour each, the experiments were initiated small quantities (5 0 µl) of drug solutions were unilaterally injected through the permanently embedded cannulas in conscious cats, experiments in our laboratory have shown by means of autoradiographic methods that the distribution of the injected volume is restricted to a well-defined area of about 2 mm in diameter following the application of 10 0 µg/5 0 µl 5-HT The experiments were performed in a 90 x 90 x 40 cm cage having a clear plexiglass front for observation and photography The day-night periodicity (8 00 a m - 8 00 p m), temperature (22°C) and light intensity in the air-conditioned, experimental room were standardized The behaviour was recorded by means of a closed TV circuit tapes provided objective and continuous records which were analysed with the aid of a standardized list of items (table 1) The observation period was divided into time-blocks of five minutes, three before and six after the injection, during every minute the presence of the items was recorded, while special symbols were used for the items 8, 10, 13, 18, 19 and 34 At the end of each time-block, a noise stimulus was presented

The following substances were injected saline (control), dopamine-HCl (DA), dexamphetamine-H_2SO_4, haloperidol, 5-hydroxytryptamine creatinine sulphate (serotonin 5-HT), para-chloro-DL-phenylalanine (p-CPA), D-lysergic acid diethylamide (LSD-25), carbamyl choline chloride (carbachol) and procaine All drugs were dissolved in saline and adjusted to pH 4-5 apart from haloperidol which was given as Serenase ® (Janssen Pharmaceutica, Belgium) and p-CPA which was given as a suspension Every drug was tested in at least seven injection-loci of different animals The location of the needle-tips was determined by reference to the atlas of Snider et al (1964)

4 1 4 RESULTS

4 1 4 1 5-HT

A map of the injection-loci effective in eliciting the behavioural changes described below is indicated in fig 1 The behavioural symptoms evoked by 5-HT application (10 0 µg) into the anteroventral part of the caput caudati in cats are qualitatively constant These animals show many marked symptoms which can be described under five headings (a) hyperkinesias, (b) abortive and disjunctive self-directed activities, (c) "vacuum" activities, (d) choreoathetosis and (e) "conditioning" effects However, these symptoms are variable from subject to subject with respect to their frequency and intensity, results of cat no 5332, therefore, are given in detail as representative for the generally observed tendency in quantitative respects (table 2) The following is a general picture of the syndrome induced by 10 0 µg 5-HT

table 1

Ethogram of the cat: the presence or absence of the listed items was recorded during each minute of the 45 min observation period; special symbols were listed for the items 8, 10, 13, 18, 19 and 34*.

"Dynamic Units"	"Static Units"	"Sense Units"	"Specific Units"	
1. Lying	8. Head movement	14. Miosis	21. Chewing	30 Mouth-opening
2. Sitting	9 Neck tension	15. Mydriasis	22 Licking	31 Tongue extrusion
3. Standing	10. Tail movement	16 Ptosis	23. Swallowing	32. Piloerection
4 Walking	11. Forelimb extension	17. Nictitating membrane	24. Sniffing	33 Convulsion
5. Moving	12. Hindlimb extension	18 Eye-opening	25. Miaowing	34 Respiration rate
6 Exploring	13. Posture	19. Ear-movement	26 Gasping	35. Urination
7. Springing		20. Clawing	27. Staring	36. Defecating
			28. Swinging	37. Cleaning
			29 Trampling	38 Crouching
				39. Backward locomotion

* "Response Units" are the items 1-39, recorded during a noise stimulus presented at the end of each time-block (5 min).

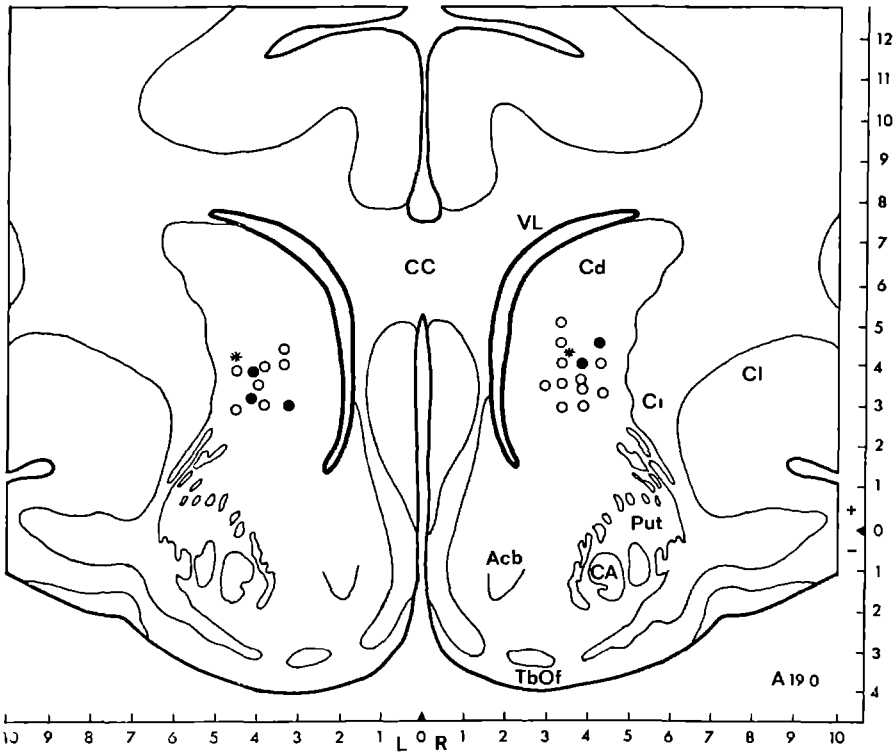

fig 1 Semi diagrammatic outline of an anterior frontal plane of the basal ganglia (A = 19 0) showing the loci, which are effective in eliciting behavioural changes following the introduction of serotonin (10 0 ug/5 0 ul) into the caput nuclei caudati anteroventralis of cats o* = effective loci found in plane A = 18 0 For abbreviations see appendix

Hyperkinesias At first there is an increase in ambulatory activities the animal alternately sits, stands and walks forward and backward, it climbs and moves at random through the cage Actually, these activities appear to be hyperkinesias rather than hyperreactivity, for the animal does not respond adequately to external stimuli Characteristic postures and movements such as the bending down posture and spontaneously occuring leapings are often displayed The hyperkinesias have a propulsive nature (obstinate progression) This is best seen when the cat coming into contact with the wall of the cage pushes against it, crawles up and displays back-rolling, trampling or extensively manipulating It is worth mentioning that the cat shows sniffing, tracing and continuously looking from side to side as though it is normally exploring, however, the

table 2

Frequencies of some items of the behavioural effects induced by application of saline (45.0 ug NaCl/5 0 µl), serotonin (10.0 µg/5 0 µl), dopamine (10 0 µg/ 5 0 µl) and carbachol (2.0 µg/5 0 µl) into the anteroventral part of the caput caudati in cat no 5332. The frequencies are indicated as follows 1 (1/time-block), 2 (2-4/time-block) and 3 (> 4/time-block). The side of occurrence of the items is shown by a (both sides), h (injection side) and c (opposite to the injection side)

COMPOUND	saline				serotonin				dopamine				carbachol			
Time-block no	4	5	6	7	4	5	6	7	4	5	6	7	4	5	6	7
"Dynamic units"																
Lying	2	2	3	0	0	0	0	0	2	2	1	1	0	1	3	3
Sitting	2	2	2	3	3	3	3	3	2	2	3	3	3	3	0	0
Standing	2	2	0	1	3	3	3	3	2	2	0	2	3	0	0	0
Moving	2	2	2	2	3	3	3	3	2	2	3	2	3	3	0	0
Exploring	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
"Static units"																
Head movement	3a	3a	3a	3a	3c	3a	3a	3a	3a	3a	3a	3a	3c	3c	2h	0
Neck tension	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2
"Specific units"																
Cleaning	3	2	0	0	3c	3a	3c	3c	2	0	3	3	3c	3	0	0
Licking	3	2	0	0	3c	3a	3c	3a	2	1	3	3	3c	3	0	0
Sniffing	2	2	0	2	3	3	3	3	2	1	3	3	3	3	0	0
Gasping	0	0	0	0	1	2	1	0	0	0	0	0	0	0	0	0
Trampling	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0
Tongue extrusion	1	0	0	0	2	1	1	2	0	0	2	2	2	0	0	0
Backward locomotion	0	0	0	0	2	2	2	2	0	0	0	0	2	0	0	0
"Sense units"																
Mydriasis	0	0	0	0	0	0	0	0	0	0	0	0	3	2	0	0
Ear-movement	2a	2a	2a	2a	2a	2a	2a	2a	2a	2a	2a	2a	2c	1c	0	0

sequence of these events is always interrupted by non-exploring activities, especially by self-directed patterns The hyperkinesias gradually decrease, but still remain present during the whole observation period

Abortive and disjunctive self-directed activities Within a few minutes after the injection the animal starts to spend considerably more time in self-directed activities These patterns are suddenly initiated and are seldom completed (abortive) Moreover, there is only gradual postural readjustment of the newly initiated patterns, sometimes, the readjustment is absolutely inappropriate (disjunctive) This is best noted when the cat jumps over from cleaning its forelimb at the one side to licking its hindlimb at the other side the animal disregards its forelimb, although this paw retains the originally outstretched position Sniffing, cleaning, licking and even biting, especially of hair and skin of its genitals, its belly and contralateral forelimb, tend to be incessant activities once started These manifestations are highly characteristic and may even result in injuries to parts of its own body If the animal is confronted with objects, it violently attempts to push, lift and bite them, often, these manipulation movements continue for a long period

"Vacuum" activities When the cat is sitting, it may suddenly stop its rhythmic turning movements or its cleaning activities and starts to display the above-mentioned manipulation patterns without the presence of any object the animal handles "non-existent" objects as if it handles real play-tools Similarly, the cat may suddenly go through all movements of searching for a prey, catching and killing it, although no prey is discernible to the observer The performance of these patterns is apparently out of context and is classified as "vacuum" activity

Choreo-athetosis During the whole observation period, especially during the fifth time-block, the cat displays non-patterned movements either involving the distal part of the forelimb or involving the entire forelimb When the cat is sitting or standing, the first type of rather slow movements, athetoid in nature, involves lifting of the forelimb from the floor, alternating hyperextension and flexion of the paw and toes, often associated with piloerection and curling of the tail The whole pattern occurs independently of the ongoing activity of the animal, the animal has no visual interest in the induced patterning of its limbs The second type of limb movements is a rapid, jerky, shaking-off movement, violent and choreiform in nature, involving the entire limb, usually, these movements follow up or interrupt the first type of movements The animal apparently forced to execute an irrelevant movement performs immediately a normal motor pattern of which the elicited movements form the initial phase very active cleaning movements are often displayed as the continuation of these originally initiated acts An example of the high frequency of these choreo-athetoid episodes is given in table 3

"Conditioning" effect In general, all mentioned symptoms persist unchanged in successive sessions An important feature however, is of particular interest

table 3

Quantitative aspects of the athetoid and choreiform episodes in cat no 5345 after microinjection of serotonin (10 0 μg/5 0 μl) into the anteroventral part of the caput caudati* Number of episodes are scored as follows 0 = none, 1 = 1-3, 2 = 4-6 and 3 ⩾ 7

post-injection time-intervals (min)	choreiform"	"athetoid"
0-3	1	1
4-6	1	2
7-9	3	3
10-12	3	3
13-15	2	3
16-18	2	1
19-21	2	1

* The number of gross limb movements vary from 1-10 per episode

There apparently develops a close association between the syndrome and the experimental environment in which the syndrome is induced when the animal returns to the experimental cage within one week, it immediately starts to display not only the intensive self-directed activities, but also the so-called "vacuum" activities This "conditioning" effect disappears after a saline injection Saline injections per se elicit a short-term increase in cleaning and licking activities, however, these symptoms disappear within a period of about 4 min

4 1 4 2 DA and dexamphetamine

When the animal is treated with 10 0 ug DA, no effects are observed apart from an increased self-cleaning and licking activity after a latency of about 10 min (table 2) Conversely, unilateral injections of 10 0 μg dexamphetamine induce intensive cleaning and licking movements, especially of the contralateral forelimb, the genitals and the middle of the lower back during the fourth period of 5 min Gradually, the whole 5-HT syndrome develops After about 10 to 12 min the animal stops these activities, shows an increasing paucity of movements and displays a profound hypokinesia, characterized by

continuous retention of the lying posture In summary, the dexamphetamine effects can be described under two headings a short-term "5-HT-like" syndrome and a long-term hypokinetic syndrome

4 1 4 3 Carbachol

Unilateral injections of 2 0 μg carbachol result in an extensive and consistent syndrome Apart from continuous cleaning, licking, especially of the contralateral side of the body, hyperkinesias and choreo-athetosis, similar to the 5-HT effects, it evokes rhythmic contralateral turning of the head, contractions of the facial muscles, fluttering of the contralateral ear, mydriasis and piloerection of the tail during the first post-injection period of about 7 min The described symptoms gradually disappear and hypokinesia becomes a significant feature, although the animal still displays rhythmic turning movements of the head (table 2)

4 1 4 4 p-CPA and LSD-25

Unilateral injections of 25 0 μg p-CPA result in rhythmic cleaning and licking patterns during the first post-injection period of about 6 min, these patterns, performed in the sitting posture, are accompanied by tongue extrusion, gasping and choreo-athetoid movements of the forelimb and do not differ from those evoked by 5-HT These activities are more and more interrupted by the arrest position at the end of this period Then, the movements become slow in nature A long-term hypokinesia starts at about 8 to 10 min after the injection, and lasts for at least 20 min The cat is lying on its belly or its side with flexed limbs and shows a disinclination to move Even when external stimuli are offered, only the eye-lids move and, in some cases, the facial muscles contract If the animal is lying in the middle of the cage, it sometimes drags itself with non-adjusted limbs towards a corner, in which it remains for the whole observation period It is important to note that all mentioned effects persist unchanged, if the experiments are performed between 9 00 a m and 11 00 a m or between 4 00 p m and 7 00 p m If performed in between, the time spent to the cleaning activities etc is much more variable and in most cases strongly prolonged The effects of unilaterally applied LSD-25 (1 0 μg) are similar to those evoked by p-CPA apart from the fact that the first phase goes on for at least 10 to 12 min In summary, p-CPA and LSD-25 induce a short-term "5-HT-like" effect followed by a long-term hypokinetic effect (table 4)

table 4

Frequencies of some items of the behavioural effects induced by application of p-CPA (25 0 µg/5 0 µl), LSD-25 (1 0 ug/5 0 µl) and haloperidol (25 0 ug/5 0 µl) into the anteroventral part of the caput caudati in cat no 5302 See table 1 for further explanation

COMPOUND	*p-CPA*				LSD-25				*haloperidol*			
Time-block no	4	5	6	7	4	5	6	7	4	5	6	7
'Dynamic units"												
Lying	0	3	3	3	0	0	3	3	3	2	3	3
Sitting	3	3	0	0	3	3	0	0	2	3	0	0
Standing	1	1	0	0	3	2	0	0	2	2	2	0
Moving	3	3	0	0	3	3	0	0	2	3	2	0
Exploring	0	0	0	0	0	0	0	0	0	0	0	0
"Static units"												
Head movement	3c	2c	1	0	3c	3a	1a	0	3a	3a	0	0
Neck tension	3	2	0	0	3	3	2	0	3	3	2	0
'Specific units												
Cleaning	3c	0	0	0	3	3	0	0	2	3	2	0
Licking	3c	0	0	0	3	3	0	0	2	3	3	0
Sniffing	3c	3	2	1	3	3	3	0	0	3	0	0
Gasping	0	2	0	0	0	0	0	0	0	0	0	0
Trampling	0	0	0	0	0	0	0	0	0	0	0	0
Tongue extrusion	1	2	0	0	0	0	0	0	0	0	0	0
Backward locomotion	0	0	0	0	0	0	0	0	0	0	0	0
"Sense units"												
Mydriasis	0	0	0	0	0	0	0	0	0	0	0	0
Ear-movement	2a	2a	0	0	2a	2a	0	0	2a	3a	2a	0

4 1 4 5 Haloperidol

Unilateral injections of 25 0 µg haloperidol evoke no abnormal symptoms during the first post-injection period of about 9 min At the end of this period, the cat displays a short-term increase in cleaning, licking and rubbing activities (about 5 min) This increased activity gradually gives way to the so-called hypokinesia, marked by the absence of any movement (table 4)

4 1 4 6 Procaine

Local application of 10 0 ug procaine immediately results in the long-term hypokinesia described under the heading of p-CPA

4 1 4 7 p-CPA, LSD-25 and haloperidol in combination with 5-HT

When p-CPA (25 0 µg) is given 15 min prior to 5-HT, the following effects are observed A normal effective dose of 10 0 µg 5-HT results in a short-term activation of cleaning, licking and sniffing patterns however, the animal resumes its characteristic lying posture very rapidly (after a latency of about 2 to 4 min) High doses of 5-HT (30 0 ug) definitely disrupt this posture and elicit the 5-HT symptoms except for the "vacuum" activities When LSD-25 (1 0 µg) is given 15 min prior to 5-HT, the normal effective dose of 10 0 µg does not induce any change in the LSD-25 evoked hypokinesia If the LSD-25 pretreatment is combined with higher doses of 5-HT (30 0 µg), the previously mentioned 5-HT syndrome is superimposed on the LSD-25 evoked hypokinesia Immediately after the injection, the animal starts to move about and displays intensive cleaning, licking and biting Suddenly, it blinks, interrupts its activity and lies down It retains this lying posture without any movement the LSD-25-evoked hypokinesia is apparently restored But then, the animal suddenly struggles to its feet and exhibits one of the 5-HT symptoms The display of these intermittent patterns goes on for a period of at least 10 min, although the duration of the hypokinetic phase more and more increases During the active phase the cat may show hyperkinesias, choreo-athetosis and intensive manipulation movements, during the passive phase the choreiform movements may also occur When haloperidol (25 0 µg) is given 20 min prior to 10 0 µg 5-HT, the hypokinesia elicited by haloperidol is immediately disrupted and the 5-HT symptoms are normally displayed, however, the hypokinesia returns within 6 to 8 min after the 5-HT injection In brief, both p-CPA and LSD-25 appear to inhibit the 5-HT effect in a competitive way, while haloperidol appears to be ineffective in this respect

4 1 4 8 p-CPA, LSD-25 and haloperidol in combination with dexamphetamine

When p-CPA (25 0 µg) is given 20 min prior to 10 0 µg dexamphetamine, the p-CPA-induced hypokinesia persists unchanged Higher doses of dexamphetamine (30 0 µg) may disrupt the p-CPA effect, but cannot induce the original dexamphetamine effects apart from the intensive cleaning, licking and sniffing activities The same holds true for the application of dexamphetamine following a pretreatment with LSD-25 (1 0 µg) using low and high doses of dexamphet-

amine respectively In contrast, application of the normal effective dose of dexamphetamine (10 0 μg) following a pretreatment with 25 0 μg haloperidol immediately results in the original dexamphetamine effects, although the intensity, frequency and duration are strongly reduced; for instance, the hypokinesia returns much faster in the pretreated animal (after 6 to 8 min) than it does in the unpretreated animal (after 10 to 12 min). In summary, both p-CPA and LSD-25 appear to induce a complete inhibition of the dexamphetamine effect, this inhibition is only slightly surmounted by high doses of dexamphetamine. Haloperidol appears to be ineffective in this respect.

4 1 5 DISCUSSION

The present study shows that 5-HT introduced into the anteroventral part of the caput caudati in cats evokes an extensive syndrome, marked by hyperkinesias, abortive and disjunctive self-directed activities, choreo-athetosis and "vacuum" activities. Apart from quantitative fluctuations, this syndrome is highly reproducible and qualitatively constant from subject to subject. The quantitative variability of these symptoms may reflect the influence of genetic and constitutional characteristics (the cats are not derived from a standard stock) and of internal variables such as circadian and ultradian rhythms (Reis et al , 1969) The induced effects appear to be 5-HT-specific in view of the following facts. (a) the inhibitor of tryptophan hydroxylase and selective depletor of 5-HT, p-CPA, completely prevents the 5-HT-induced syndrome when normally effective doses are used· high doses of 5-HT disrupt the hypokinesia evoked by p-CPA indicating that the receptive sites are still sensitive to 5-HT; (b) it is impossible to ascribe the syndrome to activation of DA-sensitive sites, for DA does not induce any effect comparable with that of 5-HT In addition, the 5-HT syndrome is not prevented by a pretreatment with the competitive DA antagonist, haloperidol.

It is known that 5-HT terminals are present within the neostriatum of rats and other mammals (Fuxe et al., 1968) Although it has been argued that these terminals in the rat belong to neurons arising from 5-HT-containing cell bodies in the raphe nuclei (Andén et al , 1966), other workers have argued that these terminals in the cat and monkey belong to neurons arising from the nucleus raphe linearis, nucleus paranigralis and other minor cell groups located in the ventromedial tegmental area below the level of the third root fibres (Parent et al , 1969, Poirier et al., 1967). It is reasonable to suggest that at least a part of the described 5-HT symptoms is due to the activation of the postsynaptic structures of these axons, however, the possibility that 5-HT postsynaptic structures of other axons are involved should not yet be ruled out in view of the lack of histochemical studies of 5-HT topography within the forebrain of the cat.

A reconstruction of the effective area leads to the conclusion that it is identical to the so-called inhibiting anteroventral area described by Liles et al. (1969b). With respect to the area effective in evoking the 5-HT syndrome, it is worth mentioning that injections into the rostromedial part of the caput caudati are ineffective (see 3 4)

Dexamphetamine evokes symptoms similar to those evoked by 5-HT, although the duration is somewhat decreased It is known that dexamphetamine mainly interferes with DA in the neostriatum (Randrup et al., 1970); however, Fuxe et al. (1970) have recently shown that dexamphetamine may also induce a release of extragranular 5-HT It is reasonable to suggest that the dexamphetamine symptoms elicited from the anteroventral area are mainly caused by this effect (a) the dexamphetamine effect mimics the 5-HT effect, although DA appears to be ineffective, (b) the effects of normally effective dexamphetamine doses are completely blocked by a p-CPA pretreatment, (c) high doses of dexamphetamine disrupt the p-CPA hypokinesia only partially and (d) haloperidol does not inhibit the dexamphetamine syndrome. In conclusion, dexamphetamine appears to activate 5-HT-sensitive sites, either directly or indirectly. Although a number of indirect lines of evidence suggests that the behaviour induced by intraperitoneal injections of dexamphetamine is mainly dependent on cerebral DA (Randrup et al., 1970), our data indicate that activation of 5-HT stores in specific parts of the brain may also be involved in the appearance of the dexamphetamine-induced behavioural patterns In view of these considerations, it is important to note that chronic methamphetamine intoxication in cats induces a number of symptoms which show a remarkable resemblance to the 5-HT syndrome, especially the self-directed activities and the so-called "conditioning" effect (Ellinwood et al , 1970a, 1970b and 1971). Apparently, LSD-25 locally introduced into the 5-HT-sensitive area induces two kinds of effects a "5-HT-like" syndrome and a hypokinetic syndrome. Although LSD-25 was previously regarded as a 5-HT antagonist on the basis of studies in peripheral tissues (Garattini et al , 1965), it has been recently argued that LSD-25 may have a "5-HT-like" effect at the postsynaptic receptors on the one hand and may specifically inhibit 5-HT neurons on the other hand (Aghajanian et al., 1970, Aghajanian, 1972; Andén et al , 1968). In our study, the "5-HT-like" syndrome evoked by LSD-25 seems to support the hypothesis of a short-term activation of postsynaptic 5-HT-sensitive sites. Conversely, the competitive inhibition of the 5-HT effects following a LSD-25 pretreatment appears to emphasize the antagonistic action of LSD-25 (Boakes et al , 1970) In view of the finding that LSD-25 evokes a powerful inhibition of the rate of firing of single 5-HT raphe neurons, it might be speculated that the LSD-25-induced hypokinesia is produced by some sort of neuronal feedback mechanism in which postsynaptic neurons may regulate the firing activity of the 5-HT-containing neurons (Aghajanian, 1972) On the other hand, it might be speculated that the LSD-25-induced hypokinesia is produced by a local

anesthetic effect, for LSD-25 appears to depress neurons directly by local anesthesia (Toman et al , 1968), the resemblance to the procaine-induced hypokinesia would support this However, it remains to be seen which mechanism is involved

The standard cholinomimetic drug, carbachol, also evokes a short-term "5-HT-like" syndrome followed by a hypokinetic syndrome On the basis of studies in guinea pig ileum, fundus of the rat stomach, etc , it is known that the 5-HT effect mimics the acetylcholine effect and is blocked by atropine, accordingly, it has been suggested that 5-HT acts through acetylcholine release However, some data strongly contradict this hypothesis for instance, 5-HT still remains effective in tissues such as rat duodenum and rat colon in the presence of atropine (for references Garattini et al , 1965) Our results cannot give any indication of the mechanism involved at this level of the brain A study of the actions of p-CPA and atropine-like substances on the 5-HT and carbachol responses might provide more information concerning this mechanism The interpretation of our results is further complicated by the fact that some symptoms such as the strong contralateral tendency of the movements show similarities with the syndrome induced by DA application into the rostromedial area of the caput caudati (Cools et al , 1970, see 3 1)

Although the role of 5-HT and its relation to behavioural changes has been extensively studied in animals, its functional role is far from clear (Aprison et al , 1972) Using indirect manipulation techniques such as changing the content of the whole cerebral 5-HT by means of the 5-HT precursor, 5-hydroxy-tryptophan, or the 5-HT depletor, p-CPA, many authors have established a relationship between cerebral 5-HT and sleep, sexual, agressive and learned behaviour (Aprison et al , 1972, Delorme et al , 1966, Ferguson et al , 1970, Tenen, 1967) However, the 5-HT syndrome locally induced in the caudate nucleus of cats appears to be absolutely unrelated to the effects induced by systemic injections These differences emphasize that the indirect manipulations of the whole cerebral 5-HT content does not tell us much about the mechanisms involved in the relationship of 5-HT at specific levels of the brain and behaviour, however, they may provide useful information, if these studies are combined with specific brain lesions of 5-HT-containing cells or fibre systems in well-defined areas (Harvey et al , 1963, Lints et al , 1969)

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4 2 THE INTERDEPENDENCY OF ELECTRICALLY EVOKED EFFECTS AND SEROTONIN-INDUCED BEHAVIOUR THE INHIBITORY ROLE OF SEROTONIN

4 2 1 ABSTRACT

Behavioural effects of electrical stimulation of the anterior part of the caput caudati have been studied in freely moving cats in chronic experiments Electrically evoked effects were also studied in animals locally pretreated with serotonin (5-HT), para-chlorophenylalanine (p-CPA), D-lysergic acid diethylamide (LSD-25), procaine, dopamine (DA) and saline Our data show (a) that the "contralateral" syndrome elicited from the anteroventral part of the caput caudati is facilitated by 5-HT and inhibited by p-CPA, LSD-25 and procaine, (b) that the "5-HT-like" syndrome elicited from the same area of the brain is inhibited by p-CPA, LSD-25 and procaine, and (c) that the "ipsilateral" syndrome also elicited from this part of the brain is inhibited by 5-HT and procaine, but uninfluenced by p-CPA and LSD-25, none of the electrically evoked responses are influenced by DA or saline
It is suggested that the system involved in the process of evoking both the "contralateral" and the "5-HT-like" syndromes exerts an inhibitory influence upon the system involved in the process of evoking the "ipsilateral" syndrome, and that 5-HT plays an important role in this inhibitory mechanism

4 2 2 INTRODUCTION

Recently, we have demonstrated that serotonin (5-HT) unilaterally introduced into the anteroventral part of the caput caudati in cats resulted in a 5-HT-specific syndrome, marked by hyperkinesias, obstinate progression, abortive and disjunctive self-directed activities, choreo-athetosis, "vacuum" activities and a "conditioning" effect (Cools, 1973b,see 4 1) 5-HT normally occurs in terminals of the neostriatum (Anden et al , 1966), these terminals in the cat belong inter alia to neurons arising from the nucleus raphe linearis, nucleus paranigralis and other minor cell groups located in the ventromedial area below the level of the third root fibres (Parent et al , 1969, Poirier et al , 1967) Evidence from a variety of sources indicates a neurotransmitter role for 5-HT in the brain (Aghajanian, 1972, Aprison et al , 1972, Bloom et al , 1972, Garattini et al , 1965, Heller, 1972) According to the results of Herz et al (1968), inhibition is the most consistent effect of iontophoretically applied 5-HT on the activity of single neurons in the neostriatum Accordingly, it seems reasonable to assume that the inhibition of the neuronal activity induced by 5-HT might underlie the 5-HT-specific syndrome Indeed, Mettler (1967) has reported that diffuse lesions in the caudate nucleus result in symptoms such

as hyperkinesias, obstinate progression, self-directed activities, manipulation and "vacuum" activities.
As electrical stimulation with carefully controlled stimulus variables induces effects due to activation of either facilitating or inhibiting neuronal elements, it is of great interest to consider the effects elicited by this technique. In the present study, therefore, we have investigated whether electrical stimulation of the 5-HT-sensitive area within the caudate nucleus of cats results in 5-HT-like responses, and whether these responses are influenced by the presence of 5-HT in this area The data reported here show that electrical stimulation of the mentioned area induces different syndromes depending on the sites of the stimulated electrodes within this area Moreover, our results show that one group of the electrically evoked symptoms is facilitated by the local application of 5-HT, while another group of electrically evoked responses is just inhibited by the local application of 5-HT. apparently, 5-HT plays an important role in the anteroventral part of the caput caudati in cats.

4 2 3 METHODS

Subjects. 22 male cats, ranging in weight from 2 5 to 3.5 kg, were used in these experiments. All animals were maintained on an ad libitum feeding schedule throughout the experiments. The temperature (22° C) and day/night periodicity were standardized.
Surgical procedures. Firstly, double barrelled, stainless steel cannulas were implanted stereotaxically into both the right and left caudate nucleus as described in previous publications (Cools et al., 1970, see 3 1 3), (co-ordinates were chosen according to the atlas of Snider et al. (1964): A = 17-19; L=3-5; H=14-16). Secondly, insulated stainless steel electrodes, 0.35 mm in diameter, impedance of 20 kΩ to 30 kΩ and bared about one mm from the tip, were implanted: a rostral-caudal and a medial-lateral couple of electrodes were placed around each injection-locus; following Laursen (1963), the tips were placed two mm apart (22 animals, 88 electrode-couples) After the implanted electrodes had been connected to a receptacle (a slightly modified Amphenol connector, type 222-3-2-N, Rodelco), the unit was surrounded by a teflon ring and mounted on the skull just above the frontal sinus by means of galvanized screws The general procedure employed did not differ from that employed by Reeves et al (1968).
Experimenatal procedures. The experiments were performed in a 90 x 90 x 40 cm cage having a clear plexiglass front for observation and tape-recording. In general, the behavioural effects were recorded by a closed TV circuit; the tapes provided objective and continuous records which were analysed with the aid of a standardized list of items (see 4.1.· table 1). In the electrical stimulation studies, the electrodes were stimulated with bipolar stimuli consisting of

30 sec trains of rectangular, biphasic pulses of 0 5 msec duration and a frequency of 20/sec, the intensity varied from 100 μA to 600 μA, most often from 100 μA to 400 μA In the chemical stimulation studies small quantities (5 0 μl) of the following compounds were given unilaterally through a needle which extended into the brain tissue 2 mm below the tip of the embedded cannulas saline (NaCl 45 0 μg), 5-hydroxytryptamine creatinine sulphate (serotonin (5-HT) 10 0 μg), D-lysergic acid diethylamide (LSD-25, a possible 5-HT-receptor agonist (Aghajanian, 1972) 1 0 μg), para-chloro-DL-phenylalanine (p-CPA, a potent inhibitor of 5-HT synthesis (Koe et al , 1966) 25 0 μg), dopamine-HCl (DA 10 0 μg), and procaine-HCl (10 0 μg) The compounds were dissolved in saline and adjusted to pH 4-5 apart from p-CPA which was given as a suspension, in preliminary experiments, it was found that the above mentioned pH had no influence on the induced effects All substances were injected in at least 6 injection-loci in different animals The maximum number of injections per cannula was restricted to eight

After habituation of the cat to the cage and connection cable during two sessions of one hour each, the experiments were initiated In the first group of experiments, the motor responses elicited by electrical stimulation were analysed in detail The recording period of 150 sec was divided in a pre-stimulation period (60 sec), a stimulation-on period (30 sec) and a post-stimulation period (60 sec), during these periods the presence or absence of each item was registered, while special symbols were listed for the items 8, 10, 13, 18, 19 and 34 (see 4 1 table 1) As initial postures of the cats determined the elicited motor responses to a large degree, stimuli were only applied to animals which were lying in a normal posture flexed fore- and hindlimbs, normal neck tension and open eyes, no stimuli were applied to animals which were moving or sleeping All stimuli were delivered in at least 6 different animals In the second group of experiments, the influence of chemical stimulation upon electrical stimulation was investigated Firstly, the effectiveness of locally applied substances was determined according to previously described methods (Cools et al , 1970, see 3 1) The appearance of the drug-specific syndromes which have been reported in extenso (Cools, 1973b, see 4 1), were used as test-parameters Secondly, subthreshold and threshold intensities were given to animals locally pretreated with the above-mentioned substances at 10 min after the injection, in the case of LSD-25 and p-CPA, they were given 20 min, 30 min and 40 min after the injection as well Control stimulation was delivered 10 min before the injection Both subthreshold and threshold values were determined in four sessions during two successive days, the subthreshold intensity was determined by testing an intensity of 50 μA, 100 μA or 150 μA lower than the threshold intensity effective in evoking movements, and selected according to the following criteria absence of these movements, and presence of only after-stimulus effects The criteria for determining the influence of the substances on electrical stimulation effects

are described in the results section After finishing the stimulation experiments, electrolytic lesions of the stimulation points were made by passing an anodal DC current of 1 0 mA for 15 sec.
Histological procedures. After completion of the experiments, the cats were sacrificed under anesthesia: i.e. perfused through the heart with saline and subsequently with 10% formaldehyde solution. The brains were removed and fixed in 4% formaldehyde solution. For the precise identification of the loci, 40 μ frontal sections of the brain were made and stained with acidified 0.25% cresyl violet. The location was determined by reference to the atlas of Snider et al. (1964).

4.2 4. RESULTS

4.2.4.1. Electrical stimulation

A. Stimulation of 38 couples (59.3%; 10 animals) resulted in the following symptoms. The animals maintained the lying posture during the first stimulation period of 0-20 sec. After this period, the animals sometimes stood up, walked around and lay down. Rhythmic movements of the head towards the stimulated side appeared independent of the body position in 73.7%, while non-rhythmic movements of the head towards this side appeared in the remaining group; the neck tension remained normal during these movements. Within a period of 5-20 sec after the stimulus-start, contractions of the facial muscles and turning of the eye-balls appeared in 26.3% of the tested cases. Alternating hyperextension and flexion movements of the ipsilateral forepaw and toes (athetoid in nature) and rapid, jerky, shaking-off movements involving the entire forelimb (choreiform in nature) were present during the whole stimulation-on period in 73.7% of the tested couples; in 46.5% of this group, these movements also appeared in the contralateral forelimb. Pupillary dilatation was noted after a latency of 20-30 sec following the stimulus-start in 21.1% of the tested cases; ptosis and contractions of the contralateral nictitating membrane were not observed. Fluttering of both ears was present in all experimental animals in this group. In 26.3% of the cases, intensive licking and cleaning activities, especially of the genital region, started after a latency of 0-20 sec after the stimulus-start, and lasted longer than the stimulation-on period. None of the remaining items mentioned in table 1 (see 4.1.) were more than incidental observations: chewing (10.5%), swallowing (5.3%), sniffing (10 5%), miaowing (18.5%) and trampling (3.3%). In view of the ipsilateral turning movements the whole stimulation effect is defined as the "ipsilateral" syndrome.
B. Stimulation of 16 couples (25 0%; 6 animals) resulted in a so-called "contralateral" syndrome. Normally, these animals maintained the lying posture

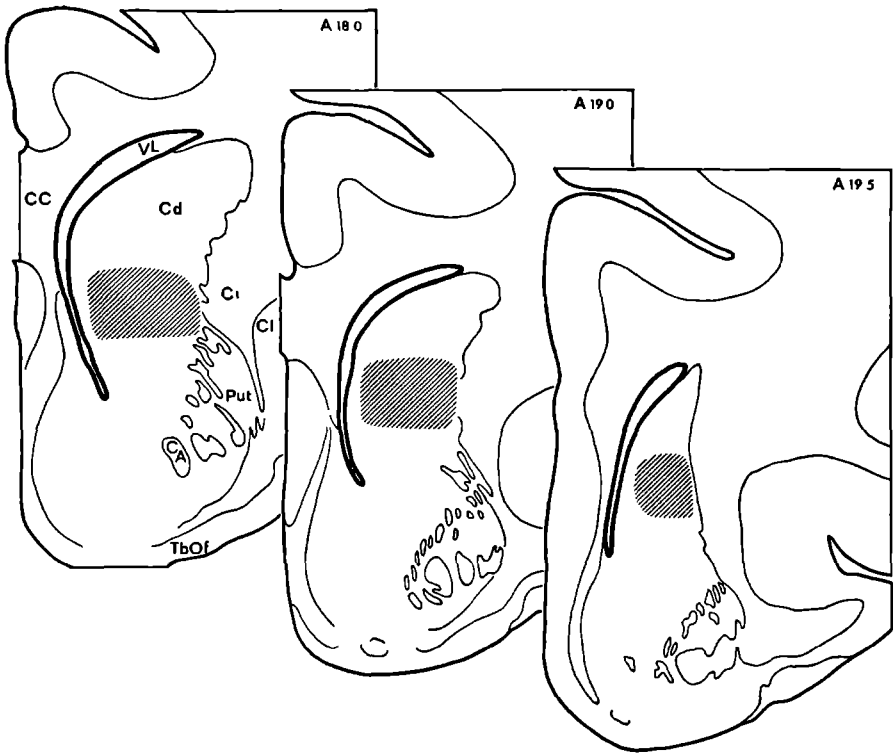

fig 2 Semi-diagrammatic outlines of three anterior frontal planes of the basal ganglia (A = 18 0, 19 0 and 19 5) showing the areas from which the syndromes described in the text are elicited The shaded areas cover the sites of 84 electrode-couples For abbreviations see appendix

during the whole stimulation period; one animal started to circle contralaterally. Exploring and springing movements were not observed. After a latency varying from 0-15 sec after the stimulus-start rhythmic movements of the head towards the non-stimulated side occurred in 75.0% of the cases, non-rhythmic contralateral movements of the head appeared in the remaining group. The neck tension remained normal during these movements. The above-mentioned choreo-athetoid movements of the forelimbs were observed in 50 0% of this group. Within a period of 10-20 sec after the stimulus-start contractions of the contralateral facial muscles and turning of the eye-balls appeared in all animals which showed the rhythmic movements of the head. Pupillary dilatation was noted after a latency of 20-30 sec after the stimulus-start in 43.8%; ptosis and contractions of the contralateral nictitating membrane were not

observed, while fluttering of both ears was noted in all experimental animals in this group Piloerection especially of the tail appeared in 87 5% of the tested cases None of the remaining items were more than incidental observations

C Stimulation of 22 couples (32 8%, 6 animals) resulted in a so-called "5-HT-like" syndrome The animals alternately sat, stood, walked, climbed and moved at random through the cage Characteristic postures and movements such as the bending down posture and leaping were often displayed The cats coming into contact with the wall of the cage pushed against it, crawled up and displayed backrolling, trampling or manipulating Sniffing, cleaning, licking and biting, especially of their genital regions, were incessant activities once started These patterns were suddenly initiated and seldom completed, moreover, there was only gradually postural readjustment to the newly initiated patterns Sometimes, the readjustment was absolutely inappropriate When the cat was sitting, it might suddenly stop its cleaning activities and start to display complex movements the animals handled "non-existent" objects as if they handled real play-tools The performance of these patterns was apparently out of context, and was classified as "vacuum" activity When the animal was sitting, rhythmic contralateral turning of the head was often seen During the whole stimulation-on period the so-called choreo-athetoid movements were irregularly shown Pupillary dilatation and piloerection, especially of the tail, were present during the whole stimulation-on period, gasping and tongue extrusion were observed in one case In general, this syndrome is identical to that evoked by the local application of 5-HT which is described in extenso elsewhere (Cools, 1973b, see 4 1)

D From the remaining 12 couples (18 9%, 6 animals), stimulation of 4 couples (6 3%) resulted in a syndrome, marked by cleaning activities, intensive cleaning and licking activities, especially of the ipsilateral hindlimb, started without any delay and lasted longer than the stimulation-on period ("cleaning" syndrome) Stimulation of 3 other couples (4 7%) resulted in myoclonic epilepsy after a latency of 10-20 sec the animals showing contractions of the facial muscles in a high intensity, suddenly extended all limbs and made clonic movements generalized convulsive seizures occurred in a high intensity These seizures were accompanied by strong salivation At the end of this attack, the animals remained immobile for a long time, sometimes a second attack appeared after the stimulus-stop Stimulation of 1 couple (1 6%) resulted in a hypokinetic syndrome the animal was lying without any spontaneous movement, lost its neck tension and failed to respond to acoustic stimuli for a long time Stimulation effects of the remaining electrode-sites were not uniform

Summarizing, three main effects were observed following electrical stimulation of different brain sites within the anteroventral part of the caput caudati of cats (a) an "ipsilateral" syndrome, marked by ipsilateral turning of the

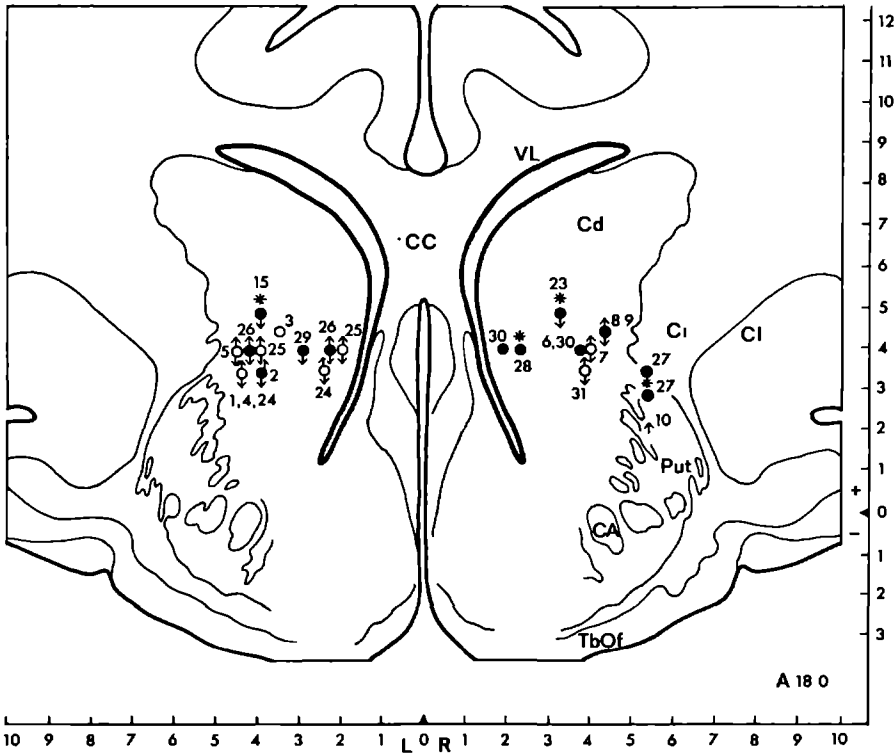

fig 3 Semi-diagrammatic outline of an anterior frontal plane of the basal ganglia (A = 18 0) showing the sites of stimulation points producing the rhythmic "ipsilateral" syndrome (rhythmic ♀ and ♀ ; non-rhythmic o), the "contralateral" syndrome (rhythmic ● , and non-rhythmic ●), the 'serotonin-like" syndrome (●) and the "cleaning" syndrome (), see also fig 2 The points marked by an asterik are found in plane A = 18 5

head, choreo-athetosis of the ipsilateral forelimb and associated effects, (b) a "contralateral" syndrome, marked by contralateral turning of the head, choreo-athetosis of the forelimbs and associated effects, and (c) a "5-HT-like" syndrome

No correlation between the threshold intensity and the evoked syndromes was found In general, animals showing motor responses during the stimulation-on period also showed after-stimulus effects In the case of the lateral syndromes, these effects consisted of a short-term fixation of the head in the forced direction and were followed by turning towards the opposite side, activities such as tongue extrusion, licking and miaowing appeared 3-15 sec

after the stimulus-stop. In the case of the "5-HT-like" syndrome, the cleaning activities remained present for a long period after the stimulus-stop; sometimes these animals continued these movements for more than 10 min. All the above-mentioned syndromes persisted unchanged in four successive sessions, although the intensity and the frequency of these symptoms varied. Re-stimulation of initially effective points resulted in the re-appearance of the effects when a time-delay of at least 10 min was used. All electrode-tips of the tested couples were located within the shaded areas shown in fig 2. In order to give an impression of the distribution of the sites effective in evoking the different types, the sites of 31 electrode-tips are shown in figs 3, 4 and 5: apparently, the stimulation points effective in eliciting different syndromes were scattered at random within the same area.

4.2.4.2. The role of 5-HT in electrical stimulation

In view of the fact that the effects induced by local application of the drugs mentioned in the methods were described earlier (Cools, 1973b; see 4.1.) only a brief survey is given here.
Unilateral injections of 5-HT resulted in a long-term syndrome (15 min), marked by hyperkinesias, obstinate progression, abortive and disjunctive self-directed activities, choreo-athetosis and "vacuum" activities.
Unilateral injections of p-CPA and LSD-25 induced a short-term "5-HT-like" syndrome (about 6 min) followed by a long-term hypokinetic effect (20 min). Apart from an increased self-cleaning and licking activity after a latency of about 10 min, no effects were elicited by the application of DA.
Finally, local application of procaine immediately resulted in a long-term hypokinesia.
Although the frequency and intensity of the induced syndromes varied strongly in each animal, the effects persisted unchanged in 90.5% of the tested loci (40) during two successive sessions in three weeks; the effects elicited from two loci were non-serotonergic. All sites of the needle-tips were located within the shaded areas shown in fig 2.
Animals in which both electrical and chemical stimulation produced the "ipsilateral", "contralateral", "5-HT-like" and 5-HT syndromes respectively were used in the chemical-electrical stimulation study (18 animals; 36 injection-sites; 72 electrode-couples). The criteria for determining the influence of the drugs on the electrical stimulation effects were as follows: (a) appearance of the characteristic symptoms during *subthreshold* stimulation of locally pre-treated animals (facilitation); (b) no reactions during *threshold* stimulation of locally pretreated animals (inhibition); and (c) no change in the characteristic symptoms during *threshold* stimulation of locally pretreated animals (in-effectiveness).

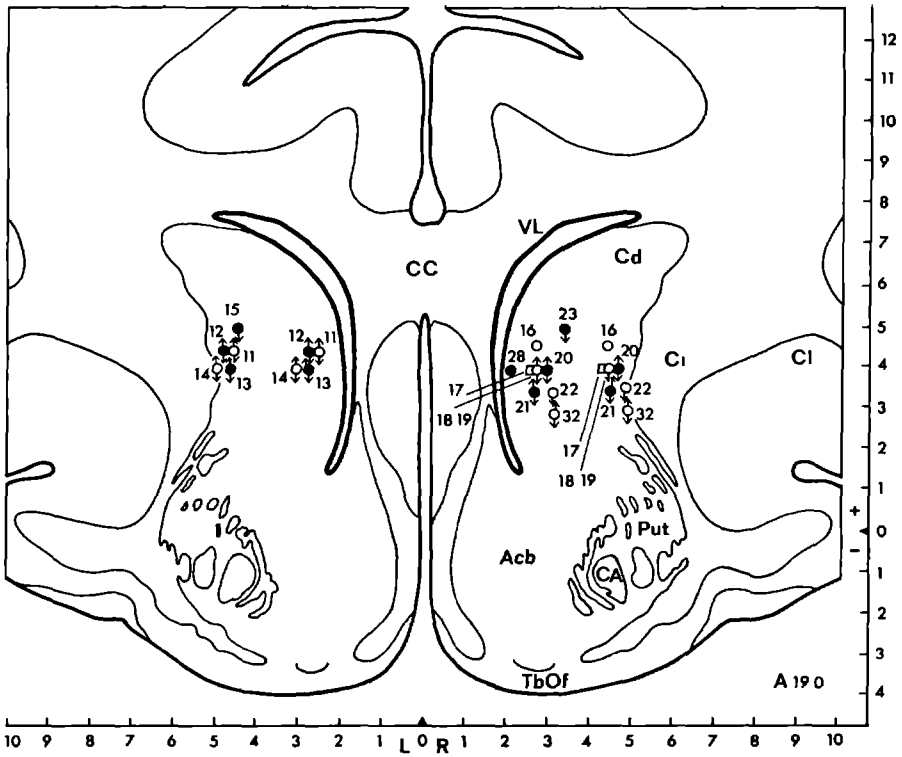

fig 4 Semi-diagrammatic outline of an anterior frontal plane of the basal ganglia (A = 19 0) showing the sites of stimulation points producing the "ipsilateral ' syndrome (rhythmic ⇕ and ⇕ , non-rhythmic o), the "contralateral" syndrome (rhythmic ⇕ , non-rhythmic ●), the "serotonin-like" syndrome (⇕) and myoclonic epilepsy (□), see also fig 2

Firstly, 5-HT (n = 8) resulted in a facilitation of the syndrome classified as the "contralateral" syndrome Both p CPA (n = 6) and LSD-25 (n = 6) resulted in a time-dependent suppression of this electrically evoked syndrome (inhibition) (tables 5 and 6) Coagulation of these points induced behavioural changes earlier determined as the "ipsilateral" syndrome

Secondly, 5-HT injections (n = 12) resulted in an inhibition of the electrically evoked "ipsilateral" syndrome p-CPA (n = 6) and LSD-25 (n = 6) had no influence at all upon this electrically evoked syndrome Coagulation of these points induced behavioural changes earlier determined as long-term hypokinesia

table 5

The time-dependent effects of intracaudate administered p-CPA (25 0 ug) upon electrical stimulation effects evoked from the anteroventral part of the caudate nucleus in cats

Cat no	behavioural effects of electrical stimulation at pre- and post-injection time-intervals (min)				
	—10	10	20	30	40
5343	abc	ab	o	ab	abc
5318	abc	a	o	a	ab
5332	abc	ab	o	ab	abc
5342	abc	ab	o	a	abc
5339	abc	ab	o	o	abc
5354	abc	abc	o	ab	abc

a = contralateral turning of the head
b = choreo-athetosis
c = licking, sniffing and cleaning

table 6

The time-dependent effects of intracaudate administered LSD-25 (1 0 μg) upon electrical stimulation effects evoked from the anteroventral part of the caudate nucleus in cats

Cat no	behavioural effects of electrical stimulation at pre- and post-injection time-intervals (min)				
	—10	10	20	30	40
5300	abc	o	o	a	ab
5287	abc	o	o	a	ab
5294	abc	o	o	o	a
5290	abc	o	o	a	a
5094	abc	o	o	a	ab
5075	abc	o	o	a	ab

a = contralateral turning of the head
b = choreo-athetosis
c = licking, sniffing and cleaning

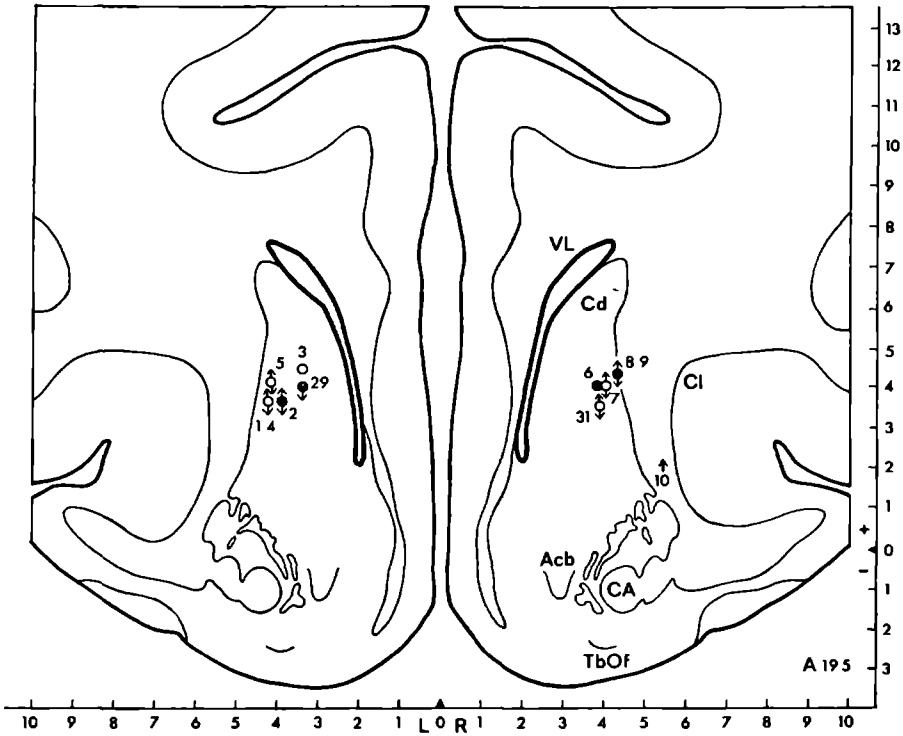

fig 5 Semi-diagrammatic outlines of an anterior frontal plane of the basal ganglia (A = 19 5) showing the sites of stimulation points producing syndromes mentioned in fig 3

Thirdly, the influence of 5-HT injections (n = 8) upon the electrically evoked "5-HT-like" syndrome could not be measured in view of the long-term after-effects of the control stimulus delivered 10 min before the local injection However, both p-CPA and LSD-25 strongly inhibited the "5-HT-like" syndrome evoked by threshold stimulation (inhibition) In addition, coagulation of these points resulted in behavioural changes earlier determined as the "ipsilateral" syndrome, apparently, both the "contralateral" syndrome and the "5-HT-like" syndrome were closely related to each other

Fourthly, unilateral injections of DA (n = 8) and saline (n = 8) did not have any effect upon the responses evoked by subthreshold or threshold stimulation (ineffectiveness)

Finally, the local application of procaine (n = 8) inhibited the electrically evoked effects in all experiments, and produced a long-term hypokinesia.

The above-mentioned influences of 5-HT, DA, procaine and saline upon the electrical stimulation effects were determined at 10 to 12 min after the injection

4 2 5 DISCUSSION

Intermediate frequency stimulation (20/sec) of the anteroventral part of the caput caudati in cats was found to elicit several types of motor responses· an "ipsilateral" syndrome (59 3%), a "contralateral" syndrome (25 0%), and a "5-HT-like" syndrome (32 8%) The elicitation of the "ipsilateral" syndrome is not only restricted to the stimulation of the caudate nucleus Dieckmann et al (1968) have reported that electrical stimulation of the putamen induced ipsilateral head turning, eye-movements, fluttering of the ears and an inactivation of motor activity as well Since these effects were also evoked from the motor area of the frontal lobe (area 6) and the centrum medianum (Hassler et al , 1967), it was suggested that the putamen might play a role in the so-called caudate-loop, in which the caudate nucleus receives an input from the diffusely projecting thalamic nuclei and feeds back modified signals to the ventral anterior nucleus of the thalamus and then to the cortex (Dieckmann et al , 1968) The fact that electrical stimulation of the caudate nucleus also produces these effects emphasizes the functional relationship between the caudate nucleus and putamen

Another important finding in our study is the "contralateral" syndrome evoked from the caudate nucleus Although this finding confirms earlier reported data of Forman et al (1957), Laursen (1963), Stevens et al (1961), and Cools (1973a, see 3 4), the most interesting fact, however, is the finding that points effective in evoking the "contralateral" syndrome and points effective in evoking the "ipsilateral" syndrome form an indistinguishable mixture throughout the anteroventral part of the caput caudati These data suggest that this part of the caudate nucleus is concerned with two separate, opposing functional systems a "contralateral" syndrome-inducing system (S1) and an "ipsilateral" syndrome-inducing system (S2) Normally, the caudate nucleus exerts a strong inhibitory influence upon the globus pallidus as shown in the electrophysiological experiments of Purpura et al (1967) and Malliani et al (1967) Although each pallidum triggers a neuronal process resulting in contralateral head movements, the symmetrical balance between both pallida suppresses the appearance of any lateral movement as pointed out by Dieckmann et al (1968) Unilateral stimulation of the caudate nucleus or putamen suppresses the pallidal activity and induces an overactivity of the contralateral pallidum resulting in the appearance of movements towards the stimulated side (S2) According to our results, lesion of S1 results in symptoms characteristic for activation of S2 apparently, S2 is only active when

S1 is suppressed In view of these data, it seems reasonable to suggest that S1 normally exerts an inhibitory influence upon S2

As shown in our experiments, electrical stimulation of some points within the anteroventral part of the caput caudati results in the so-called "5-HT-like" syndrome The symptoms differ only quantitatively from those induced by the local introduction of 5-HT into this area It is interesting to note that the yield of 5-HT-release in the lateral ventricle, following electrical stimulation of the nucleus raphe linearis intermedius or of the nucleus raphe linearis rostralis of the cat, is dependent on the frequency of the stimulation the highest yield was obtained at 20/sec as reported by Holman et al (1972), in our experiments, it was found that this frequency also induced optimal effects A similar correlation between the frequency used in midbrain raphe stimulation and behavioural effects in rats induced by 5-hydroxytryptophan was reported by Kostowski et al (1969)

Previously, we have shown that the 5-HT-induced effects were 5-HT-specific (Cools, 1973b, see 4 1) Since several symptoms such as hyperkinesias, obstinate progression, self-directed activities, manipulation and "vacuum" activities were described as consequences of caudate lesions (Mettler, 1967), we have tentatively suggested that 5-HT might have an inhibitory function at this level of the brain (Cools, 1972) Considering the above-mentioned hypothesis concerning the two separate, opposing functional systems, it seems reasonable to suggest that S1 exerts its inhibitory influence upon S2 by means of 5-HT electrical stimulation of S1 results in symptoms which are facilitated by 5-HT and inhibited by p-CPA, while electrical stimulation of S2 results in symptoms which are inhibited by 5-HT and uninfluenced by p-CPA Apparently, 5-HT activates S1 and inhibits S2

Although LSD-25 was previously regarded as a 5-HT antagonist on the basis of studies in peripheral tissues (Garattini et al , 1965), it has recently been argued that LSD-25 may have a 5-HT-like effect at the postsynaptic receptors on the one hand, and may specifically inhibit 5-HT neurons on the other hand (Aghajanian, 1972) In our study, the competitive inhibition of the electrically evoked "5-HT-like" syndrome following an LSD-25 pretreatment seems to emphasize the antagonistic action of LSD-25

As a final remark, the appearance of myoclonic epilepsy in 3 cases may be ascribed to the stimulation of afferent projections from the centrum medianum thalami, stimulation of which also results in myoclonic epilepsy as reported by Hunter et al (1949)

Summarizing, our data suggest that the system involved in the process of evoking both the "contralateral" and "5-HT-like" syndromes exerts an inhibitory influence upon the system involved in the process of evoking the "ipsilateral" syndrome, and that 5-HT plays an important role in this inhibitory mechanism

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CHAPTER 5

THE TRANSNEURONAL RELATIONSHIP BETWEEN DOPAMINE AND SEROTONIN IN THE CAUDATE NUCLEUS OF CATS

5 1 ABSTRACT

In order to study the possible transneuronal relationship between dopamine (DA) and serotonin (5-HT) mechanisms in the caudate nucleus of cats, a behavioural analysis has been made of effects brought about by simultaneously or successively given injections of DA, 5-HT, carbachol and some related compounds into the DA-sensitive caput caudati rostromedialis (CRM-area) and the 5-HT-sensitive caput caudati anteroventralis (CAV-area) in cats The data reported here show that inhibition of the 5-HT activity in the CAV-area abolishes the effects elicited by activation of the DA mechanism in the CRM-area, and that inhibition of the DA mechanism in the CRM-area does not influence the effects elicited by inhibition of the 5-HT activity in the CAV-area Furthermore, it has been found that inhibition of the cholinergic mechanism in the CAV-area abolishes the effects elicited by the activation of the DA mechanism in the CRM-area Finally, it was found that inhibition of the 5-HT mechanism in the CAV-area abolishes the effects elicited by activation of the cholinergic mechanism in the CAV-area, whereas inhibition of the cholinergic mechanism does not affect the effects elicited by activation of the 5-HT mechanism in this area
A model by which these neurotransmitter systems might operate is proposed

5 2 INTRODUCTION

Evidence has been presented that the combination of L-3,4-dihydroxyphenylalanine (L-DOPA, the precursor of dopamine (DA)), and a peripheral L-amino-acid decarboxylase inhibitor (Ro-4-4602) given to animals, not only increases the DA content of the caudate nucleus, but also decreases the serotonin (5-HT) content of this nucleus (Bartholini et al , 1968, Pletscher et al , 1969) Several possible mechanisms have been adduced to explain this effect There is some evidence that L-DOPA or its metabolite, DA, may interfere with 5-HT by inhibiting the enzymes involved in 5-HT synthesis (Jequier et al , 1969), by competing with the uptake of 5-HT into the brain and neurons (Bartholini et al , 1970), or by displacing 5-HT from its intraneuronal storage sites and then acting as false neurotransmitter (Ng et al , 1970) It remains possible, however, that the 5-HT decrease is partly due to a trans-

synaptic relationship between 5-HT-rich and DA-rich fibre systems (Heller, 1972)

Recently, it has been shown that there exists a DA-sensitive area and a 5-HT-sensitive area within the caput caudati of cats these areas are defined as the caput caudati rostromedialis (CRM-area) and the caput caudati anteroventralis (CAV-area) respectively (Cools et al , 1970, Cools, 1972a, see 3 1 and 4 1) Chemical and electrical stimulation studies have revealed that the CAV-area is concerned with two different, opposing, functional systems a "contra-lateral" syndrome-inducing system (S1) which is potentiated by locally administered 5-HT, and an "ipsilateral" syndrome-inducing system (S2) which is inhibited by locally administered 5-HT (see 4 2) Similar studies dealing with the role of DA in the CRM-area have established that the DA-sensitive CRM-area is also concerned with these systems (Cools, 1973a) In view of these data, it is attractive to assume that the DA-sensitive CRM-area is closely related to the 5-HT-sensitive CAV-area If true, the evidence for a transneuronal relationship between the DA and 5-HT mechanisms would be greatly strengthened

In the present study, therefore, an effort has been made to investigate the interdependency of both neurotransmitter mechanisms by studying the behavioural effects evoked by simultaneous chemical stimulation of the involved areas As activation of acetylcholine-sensitive sites in the CAV-area by means of carbachol elicits symptoms both characteristic for the activation of the DA mechanism in the CRM-area and characteristic for activation of the 5-HT mechanism in the CAV-area (Cools, 1973b, see 4 1), a functional study of the role of the cholinergic mechanisms is included The data reported here suggest that the three mentioned neurotransmitter systems are connected *in series*

5 3 METHODS

Experiments were performed on adult, male cats weighing 2 5 to 3 5 kg During pentobarbital anesthesia (30 0 mg/kg i p), double barrelled, stainless steel cannulas were stereotaxically implanted into the CRM-area (co-ordinates A = 14-16, L = 4-6, H = 14-16) and the CAV-area (co-ordinates A = 17-19, L = 3-5, H = 13-15) at the right side of each cat brain (Snider et al , 1964) Upon complete recovery from the anesthesia, placing responses righting and pupillary reflexes were checked, in addition, the food-intake and reactivity to visual and acoustic stimuli were estimated Experiments with normally responding cats were initiated one week after the operation

Behavioural parameters were recorded in order to measure the drug effects, an account of the experimental technique has been extensively described elsewhere (Cools et al , 1970) Small quantities of drug solutions (10 0 µl into

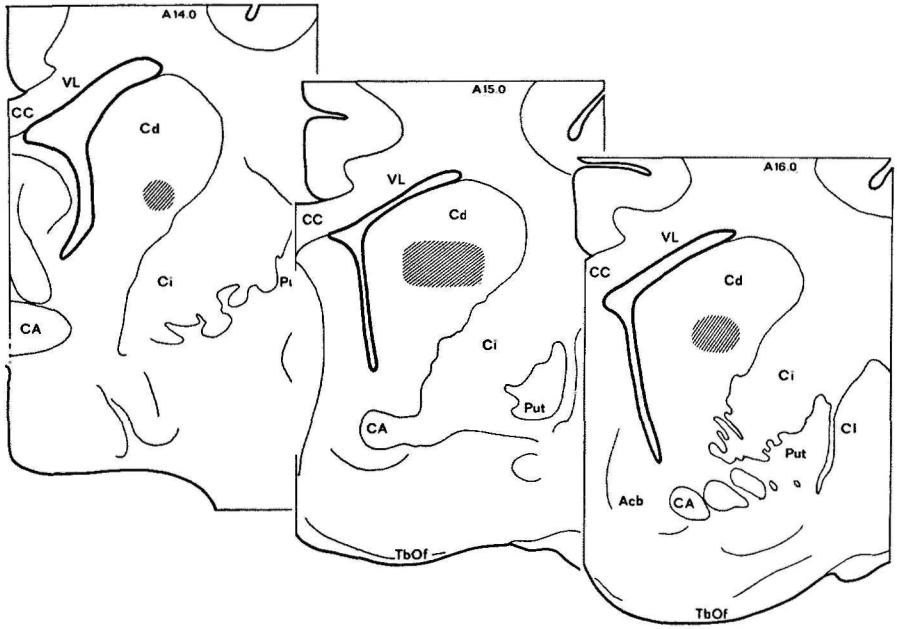

fig 1. Semi-diagrammatic outlines of three anterior frontal planes of the basal ganglia (A = 14.0, 15.0 and 16.0) showing the areas to which the injection-sites effective in eliciting the dopamine syndrome are restricted.

the CRM-area; 5.0 µl into the CAV-area) were injected through an injection needle which extended into the brain tissue 2 mm below the tip of the embedded cannulas. The following substances were used: saline (control), dopamine-HCl (DA), procaine-HCl, 5-hydroxytryptamine creatinine sulphate (5-HT: serotonin), para-chloro-DL-phenylalanine (p-CPA, a serotonergic inhibiting agent), carbamylcholine chloride (carbachol, a cholinergic stimulating agent), haloperidol (a dopaminergic inhibiting agent) and scopolamine-HBr (a cholinergic inhibiting agent). The compounds were dissolved in saline and adjusted to pH 4-5, apart from haloperidol which was given as Serenase ® (Janssen Pharmaceutica, Belgium) and p-CPA which was given as a suspension. All substances were tested in at least 8 injection-loci of different animals; the inter-trial time was one week, while each drug trial was followed by a saline trial. The maximum number of injections per cannula was restricted to eight.

Firstly, the effectiveness of different substances locally introduced either into the CRM-area (DA, haloperidol and procaine) or into the CAV-area (5-HT,

p-CPA, procaine, carbachol and scopolamine) was determined the appearance of the drug-specific syndromes, which are described in extenso elsewhere (Cools et al , 1970, Cools, 1971, 1972b, 1973a, b, see 3 1 , 3 2 , 3 3 and 4 1), were used as test-parameters

After these preliminary experiments, the mutual dependency between the DA-sensitive CRM-area and the 5-HT-sensitive CAV-area was determined by measuring the behavioural effects of combined chemical stimulation of each area (for the test-scheme used see results)

In an additional group of experiments, the mutual dependency between acetylcholine and 5-HT in the CAV-area was determined by measuring the behavioural effects of combined chemical stimulation of these mechanisms in the CAV-area

In the case that both the CRM-area and the CAV-area were stimulated, the two solutions were simultaneously given, apart from the case in which p-CPA was used this compound was given 20 min prior to the second solution In the case that the CAV-area was stimulated by two different substances, both compounds were dissolved in one solution of 5 0 µl, apart from the case in which p-CPA was used then, the p-CPA solution (5 0 µl) was given 20 min to the second solution (5 0 µl)

After completion of the experiments, the precise identification of the injection-sites was determined by reference to the atlas of Snider et al (1964) according to previously described procedures (Cools et al , 1970)

The data presented below are derived from experiments in which the injection-sites were restricted to the shaded areas shown in figs 1 and 2

5 4 RESULTS

5 4 1 SINGLE INJECTIONS

In view of the fact that the effects induced by the application of the substances mentioned in the methods were described earlier, only a brief survey is given here

A The CRM-area

DA syndrome Unilateral injections of DA (10 0 µg, n = 21) produced a "contralateral" syndrome, marked by a reduction in locomotor activity, contralateral turning of the head, choreo-athetosis of the contralateral forelimb, contractions of the contralateral facial muscles, contralateral turning of the eye-balls, fluttering of the contralateral ear, ptosis, miosis and alternating periods of rest and activity These symptoms appeared at the end of the first 5 min apart from the choreo-athetosis which already appeared in the middle of this period, they had nearly a constant frequency during the next 5 min, and disappeared during the following 5 min period

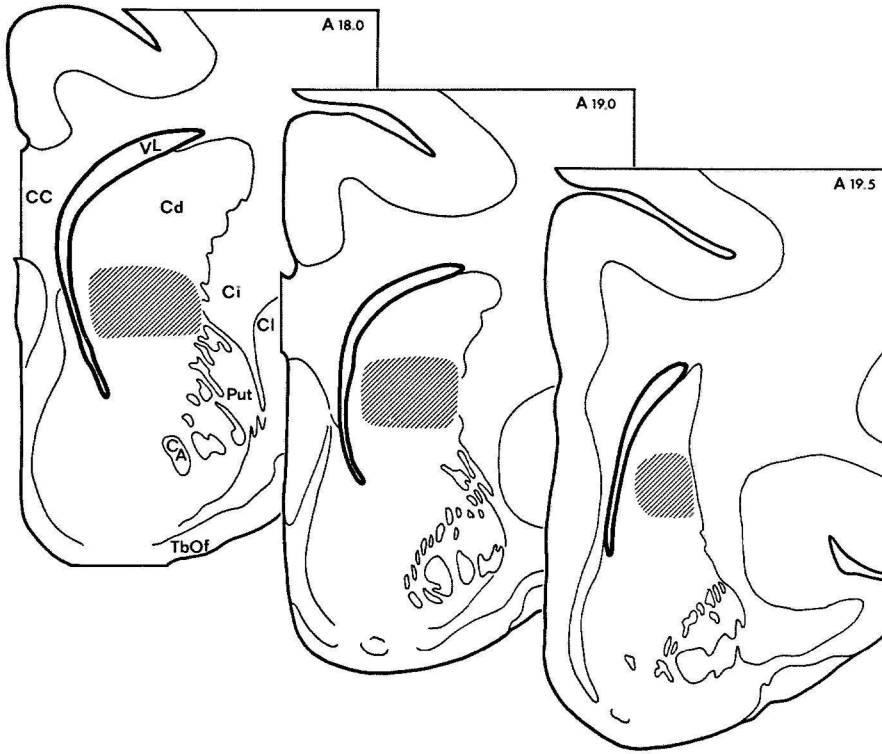

fig 2. Semi-diagrammatic outlines of three anterior frontal planes of the basal ganglia (A = 18.0, 19.0 and 19.5) showing the areas to which the injection-sites effective in eliciting the serotonin syndrome are restricted.

Procaine and haloperidol syndrome. Unilateral injections of procaine (10.0 μg; n = 22) and haloperidol (25.0 μg; n = 20) induced an "ipsilateral" syndrome, marked by ipsilateral turning of the head, ipsilateral turning of the eye-balls, ptosis, fluttering of the ipsilateral ear, contractions of the ipsilateral facial muscles and choreo-athetosis of the ipsilateral forelimb. These symptoms appeared at the end of the first 5 min, although the haloperidol effects appeared somewhat earlier; they disappeared during the following 5 min period (procaine) and 10 min period (haloperidol).

B. The CAV-area.

5-HT syndrome. Unilateral injections of 5-HT (10.0 μg; n = 15) produced hyperkinesias, abortive and disjunctive self-directed activities, intense choreo-athetosis and "vacuum" activities. This syndrome already appeared within a few minutes after the injection and lasted for at least 15 min.

p-CPA syndrome Unilateral injections of p-CPA (25 0 μg, n = 14) produced a short-term 5-HT-like syndrome of about 5-8 min followed by a long-term hypokinesia, which reached its optimum at about 20 min after the injection
CAV-procaine syndrome Unilateral injections of procaine (10 0 μg, n = 14) immediately produced a hypokinesia, lasting about 5-10 min
Carbachol syndrome Unilateral injections of carbachol (2 0 μg, n = 15) produced two types of symptoms during the post-injection period of about 7 min (a) contralateral turning of the head, contractions of the contralateral facial muscles, fluttering of the contralateral ear, piloerection and mydriasis (cf the effects evoked by DA application into the CRM-area), and (b) hyperkinesias, abortive and disjunctive self-directed activities and intense choreoathetosis (cf the effects evoked by 5-HT application into the CAV-area) These symptoms were followed by a hypokinesia, which lasted about 10 min
Scopolamine syndrome Unilateral injections of scopolamine (100 0 μg, n = 15) produced a slight hypokinesia at the end of the first 10 min after the injection, lower doses of scopolamine (10 0 and 50 0 μg) were ineffective

5 4 2 COMBINED INJECTIONS

All injections into the CAV-area of compounds interfering with either the 5-HT or cholinergic mechanisms produced their effects independent of the kind of drugs injected into the CRM-area (table 1)
Injections of carbachol (2 0 μg, n = 6) into the CAV-area of animals, pretreated with a p-CPA injection into the same area 20 min earlier, did not disrupt the p-CPA-induced hypokinesia On the other hand, a combined injection of scopolamine (100 0 μg, n = 7) and 5-HT (10 0 μg, n = 7) into the CAV-area resulted in the normal 5-HT syndrome

5 5 DISCUSSION

5 5 1 THE TRANSNEURONAL RELATIONSHIP

In the present study, it was found that behavioural effects induced by either activation or inhibition of the DA mechanism in the CRM-area were completely dominated by the effects elicited by either activation or inhibition of the 5-HT mechanism in the CAV-area In fact, interference with the DA mechanism was totally ineffective when the 5-HT mechanism was in any way disturbed, while interference with the 5-HT mechanism always resulted in the expected effects even when the DA mechanism was disturbed Apparently, the 5-HT mechanism is an indispensable link in the sequential chain of intracaudate events triggered

table 1

Behavioural effects of combined chemical stimulation of the caput caudati rostromedialis (CRM) and the caput caudati anteroventralis (CAV) in cats For description of the syndromes see text

CRM-injection	(10 0 ul)	plus	CAV-injection	(5 0 µl)	Behavioural effect		(exp)
dopamine	10 0 µg		serotonin	10 0 µg	serotonin	syndrome	(7)
haloperidol	25 0 µg		serotonin	10 0 µg	serotonin	syndrome	(7)
procaine	10 0 µg		serotonin	10 0 µg	serotonin	syndrome	(8)
dopamine	10 0 µg		p-CPA*	25 0 µg	p-CPA	syndrome	(8)
haloperidol	25 0 µg		p-CPA*	25 0 µg	p-CPA	syndrome	(6)
procaine	10 0 µg		p-CPA*	25 0 µg	p-CPA	syndrome	(6)
dopamine	10 0 µg		procaine	10 0 µg	CAV-procaine	syndrome	(7)
haloperidol	25 0 µg		procaine	10 0 µg	CAV-procaine	syndrome	(7)
procaine	10 0 µg		procaine	10 0 µg	CAV-procaine	syndrome	(8)
dopamine	10 0 µg		scopolamine	100 0 µg	scopolamine	syndrome	(8)

*p-CPA was given 20 min prior to the injection into the CRM-area

by the DA mechanism These data are in agreement with the studies of Scheckel et al (1965) who reported that systemically given L-DOPA only induces its stimulating effect when the 5-HT mechanism is unaffected
A second important finding in the present study is the fact that blockade of the cholinergic mechanism in the CAV-area results in the suppression of the effects elicited by activation of the DA mechanism in the CRM-area Thus, it appears that the cholinergic mechanism is also an indispensable link in the sequential chain of intracaudate events triggered by the DA mechanism in the CRM-area A large number of clinical and experimental studies have indicated that there exists a so-called "see-saw" in the brain with DA on the one side, and acetylcholine on the other side (Arnfred et al, 1968, Klawans, 1968, Scheel-Kruger, 1970) In contrast with these findings, our data indicate that both neurotransmitter mechanisms are co-operating in the same direction Thus, it appears that there are at least two different cholinergic mechanisms within the brain one which antagonises the DA mechanism, and one which co-operates with the DA mechanism This is in agreement with the data reported by Bartholini et al (1971) who found that systemically administered atropine decreases the DA turnover in the neostriatum of rats, while intraventricularly administered atropine does not affect the neostriatal DA turnover, on the basis of preliminary experiments, in which they found that supranigral injection of atropine caused a marked increase of the neostriatal homovanillic acid without changing the DA concentration, they suggested that the distribution of the intraperitoneally administered atropine might be such that the DA-counter-balancing cholinergic mechanism is preferentially inhibited whereas on intra-ventricular administration the drug may mainly interfere with the DA-co-operating system Indeed, Neill et al (1970) have shown that there are two opposing functional, cholinergic mechanisms within the neostriatum blockade of the cholinergic mechanism in the dorsal part produces an acquisition deficit of avoidance responses, while a similar blockade in the ventral part of this brain structure produces a facilitation of the acquisition of these responses
The third important finding in the present study is the fact that blockade of the 5-HT mechanism in the CAV-area suppresses the effects elicited by activation of the cholinergic mechanism in this area, whereas activation of the 5-HT mechanism completely surmounts the effects evoked by inhibition of the cholinergic mechanism in this area Again, it appears that the 5-HT mechanism is an essential link in the chain of intracaudate events triggered by the cholinergic mechanism

5 5 2 HYPOTHETICAL MECHANISM OF ACTION

As mentioned in the introduction the CAV-area is concerned with two systems having diametrically opposite functions a "contralateral" syndrome-inducing

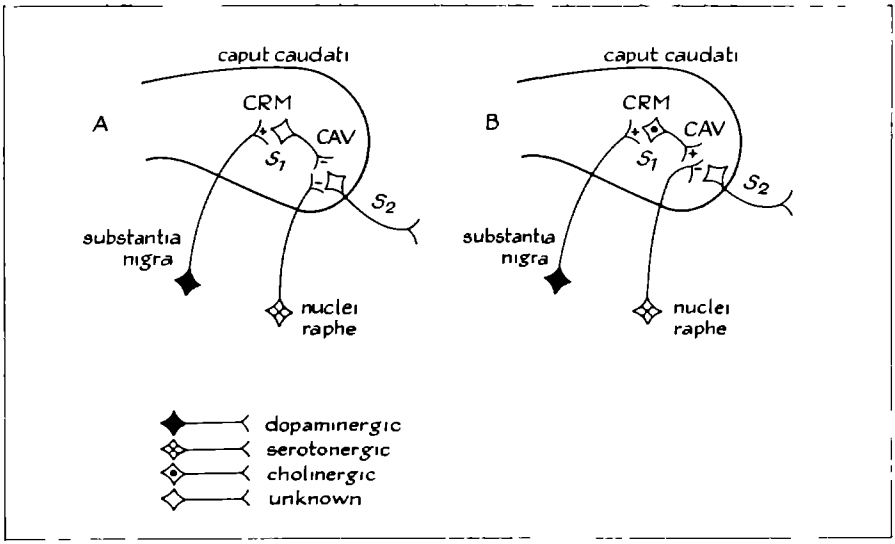

fig 3 Two models by which the dopamine, acetylcholine and serotonin mechanisms might operate in the caput nuclei caudati rostromedialis (CRM) and the caput nuclei caudati anteroventralis (CAV) S_1 refers to the contralateral syndrome-inducing system, and S_2 to the "ipsilateral" syndrome-inducing system

system (S1), and an "ipsilateral" syndrome-inducing system (S2) As S2 is only active when S1 is suppressed, and suppression of S2 does not result in effects characteristic of S1, it has been concluded that S1 normally inhibits S2 (see 4 2), furthermore, it has been demonstrated that 5-HT fulfils an important role in this inhibitory mechanism (Cools, 1972a, see 4 2) On the other hand, it has been established that the CRM-area is also concerned with these systems activation of this area by means of DA or electrical stimulation produces symptoms characteristic of S1, while lesion of this area or suppression of the DA activity in this area results in symptoms characteristic of S2 (Cools, 1973a, see 3 4) From these data, it has been suggested that the CRM-area is connected with the CAV-area by means of small inhibiting interneurons (Cools, 1972b, 1973a, see 3 3 and 3 4) activation of the DA mechanism in the CRM-area should induce activation of S1 by triggering the interneurons, which, in turn, should exert an inhibitory influence upon S2 by means of 5-HT (fig 3a)

The present findings, however, suggest that the DA mechanism in the CRM-area is indirectly connected to the 5 HT mechanism in the CAV-area by

means of a cholinergic mechanism A possible way by which the DA, acetylcholine and 5-HT mechanisms might operate is proposed to explain the above-mentioned data activation of the nigro-caudate, DA mechanism in the CRM-area may induce activation of S1 by triggering intracaudate, cholinergic interneurons, which, in turn, induce an inhibition of S2 by triggering the raphe-caudate, 5-HT neurons in the CAV-area (fig 3b) Anatomical and histochemical evidence in favour of the DA-rich, nigro-caudate fibres and of 5-HT-rich, raphe-caudate fibres is available (Hokfelt et al , 1969, Parent et al , 1969, see 2 3), whereas histochemical evidence in favour of acetylcholine-rich, intracaudate fibres has been presented (McGeer et al , 1971) Furthermore, analyses of the responses of caudate cells to iontophoretically applied DA, acetylcholine and 5-HT has yielded evidence compatible with the presented model (McLennan et al , 1966, 1967, Herz et al , 1968)

In view of the facts that (a) a large number of cells is also affected in the opposite direction by iontophoretic application of DA, acetylcholine and 5-HT (McLennan et al , 1966, 1967, Herz et al , 1968), (b) the caudate nucleus contains more putative neurotransmitters than DA, acetylcholine and 5-HT alone, and (c) the caudate nucleus has more afferent, efferent and intrinsic fibres than are shown in fig 3, it is axiomatic that the model presented only represents an oversimplified situation However, it can be concluded that there exists a close transneuronal relationship between the DA, acetylcholine and 5-HT mechanisms in the caput caudati of cats This may have the implication that a change in one particular neurotransmitter mechanism does not result in a solitary change in this mechanism, but rather in a complex of changes in all three neurotransmitter mechanisms

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CHAPTER 6

THE CAUDATE NUCLEUS RESPONSE CHAINING SYSTEM

In this chapter, it is attempted to develop the concept that the caudate nucleus has an essential role in the process of response chaining, i e breaking down previously established links between different elements of a response chain, and enabling the animal to re-establish new links between the loosened elements This concept is mostly based upon the recognition that the movements induced by either electrical or chemical activation of the caudate nucleus are discrete types of muscle contractions which, together with other types of muscle contractions, normally occur in higher complexes of behavioural activities Apart from the fact that the proposed concept accounts for most of the available data in this field, it also opens a new direction in which one may look for a more fundamental understanding of the amphetamine-induced stereotypies and psychoses

6 1 THE CENTRAL CONCEPT

The evidence presented in section 3 4 indicates that both chemical and electrical stimulation of the dopamine-sensitive area in the caudate nucleus of cats produces a "non-specific" activation of neuronal discharge within this nucleus, the term "non-specific" activation is more correct because of the non-physiological nature of the methods used
As reported in previous chapters (see 3 1 - 3 4), both manipulation techniques inter alia produce a number of contractions of different muscle groups resulting in rhythmic contralateral turning movements of the head, movements of the ears, turning of the eye-balls, unilateral ptosis, unilateral contractions of the facial muscles, etc In a normal situation, sensory stimulation never triggers such discrete contractions as isolated elements, but always as elements which are part and parcel of functional units on higher integrated levels In other words, the induced contractions appear to be merely loosened elements of a normally integrated chain of spatio-temporal combinations of muscle contractions A second characteristic property of the induced movements is their compulsive nature they are compulsive in their repetitiveness In order to understand these observations, it is necessary to consider some basic properties of the normal patterning of complex movements (for a detailed account the reader is referred to Hinde (1966)) Normally, complex movements involve a number of muscles contracting in a characteristic relationship with each other The sequence in which the muscles contract is

either completely determined, or strongly dependent on the sensory stimulation encountered during the course of ongoing contractions
In the first case, the temporal patterning elicited by environmental or interoceptive stimuli is determined from the start, and is only adjusted by stimuli received as a consequence of earlier phases of the movement In the last case, both feedback effects from the ongoing muscle contractions and exteroceptive stimuli encountered during the performance of the muscle contractions, activate the muscles contracting later in the sequence In both cases, the sequence in which the muscles contract is under control of higher co-ordinating mechanisms in which both the exteroceptive and interoceptive information is continuously integrated (Monnier, 1970) In this context, it is useful to introduce the term "target value" This can be most easily illustrated with the mechanisms underlying the stretch reflex as proposed by Hinde (1966) It is known that the sensory part of the muscle spindles, which lie parallel to the muscle fibres and their attachments, do not respond to the absolute length of the muscle, but to the difference between the length of the spindle and the length of the muscle as indicated by a local feedback system There appears to exist an "ideal" equilibrium position between both elements, this state is defined as "target value" (Hinde, 1966) Analogous to this system, it has been demonstrated that the direction of the change in complex movements is also influenced by the direction of the discrepancy between the ongoing activity and a "should be value", i e target value (Deutsch, 1960, Holst et al , 1950, Hinde, 1966) As the changeover from one activity to the next in complex movements depends on a mechanism in which both extero- and interoceptive information produces changes both in the musculature relevant to the next activity and in the musculature relevant to the first activity, the organism must also have at its disposal systems which play a part in comparing incoming information with the "ideal" link between the ongoing activity and the next activity forming the "ideal" chain In view of these considerations, the "ideal" link between two responses can be analogously defined as target value When the sensory stimulation required for the elicitation or adjustment of the next activity is absent, the "ideal" sequence is disrupted, and a tendency to repeat the ongoing activity is shown (Sherrington, cited by Hinde, 1966), Hinde, 1966)

As "non-specific" activation of the caudate nucleus produces merely loosened elements which are compulsive in their repetitiveness, it is attractive to postulate that normal activation of the caudate nucleus produces a disruption of a system in which incoming signals are compared with previously established target values, i e links between two or more responses forming an integrated sequence of elements As this concept is an inference based on knowledge which is insufficient to prove its high probability, the question to be discussed must be restricted to an examination of how well the neurobehavioural data reported earlier conform to this concept

A "Non-specific" activation of the caudate nucleus or neostriatum

It has been demonstrated that low frequency stimulation of the caudate nucleus in cats, trained to press a lever in order to get food, produces a cessation of the bar-pressing response (Buchwald et al , 1961) As the animal is unconcerned with the lever during the cessation, but exhibits activities such as licking of cream remaining in the food cup, standing, sitting, grooming and normal orienting responses, it appears that the learned sequence consisting of walking towards the lever, pressing the bar, etc , is completely disrupted during the "non-specific" activation of the caudate nucleus, although the animal remains sensitive to sensory stimulation Secondly, it is known that rats given a single footshock, while standing upright and drinking from a tube, are slow in returning to the tube and drinking when tested 24 hr later When electrical stimulation of the neostriatum follows the footshock within a short time, the rats quickly return and drink (Wyers et al , 1968, 1971) As the animal does not show the one-trial learned response chain, i e not freezing or related behaviour, but turning and drinking, it appears that "non-specific" activation of the neostriatum may even produce a retrograde disruption of the previously established chain of responses This is further supported by the experiments of Peeke et al (1971), who have demonstrated that electrical stimulation of the neostriatum also produces a retroactive impairement of an appetitively reinforced maze learning task At about the same time, Herz et al (1971) extended these data with the observation that the development of extinction of such an appetitively motivated response is similarly impaired when electrical stimulation of the neostriatum is applied after the first extinction trial In fact, these data indicate that "non-specific" activation of the neostriatum can disrupt a previously established chain of responses

B Inactivation of the caudate nucleus or neostriatum

Although neostriatal-damaged animals are not impaired in visual, olfactory and classical discrimination learning (rats Brown et al , 1938, rats Ghiselli et al , 1938, monkeys Rosvold et al , 1956, 1958, cats Thompson et al , 1961), such animals are strongly impaired in producing the reversal of an initially acquired light-dark discrimination (rats Kirkby, 1969) in fact, they produce significantly more non-correct responses than non-lesioned animals in their reversal trials These data are in agreement with those of Divac et al (1967), who have reported that the number of non-correct responses during object reversal learning in caudate-damaged monkeys is also increased in comparison with control animals Furthermore, these data are compatible with the fact that caudate-lesioned cats are unable to inhibit an instrumental feeding response in passive avoidance situations, although they are able to acquire the instrumental feeding response itself (cats Fox et al , 1964, rats Mitcham et al , 1972, rats Winocur et al , 1969) In other words, it appears that an established spatio-temporal combination of post-operationally learned motor patterns

cannot be dissolved in animals with lesions in the neostriatum, the ability to create completely new links between two or more elements, however, remains unaffected The first conclusion is in agreement with the finding that neostriatal-damaged animals are impaired in the acquisition of spatial alternation, delayed response and delayed alternation response (monkeys Battig et al , 1960, rats Chorover et al , 1963, monkeys Cohen, 1972, rats, cats and monkeys Divac et al , 1967, 1971, Divac et al , 1972, rats Gross et al , 1965, monkeys Rosvold et al , 1956, see also Potegal, 1972) i e the number of trials required for the acquisition of the delayed responses is significantly increased, whereas the number of non-correct responses, i e responses during the time-interval, is also increased In this context, it is worthy of mention that an increase in the neostriatal dopamine activity in cats, i e an increase in the neuronal activity in this part of the brain, produces effects diametrically opposite to those produced by lesions an improvement in the performance of the delayed response (Kitsikis et al , 1972) Finally, it has been shown that neostriatal-lesioned rats and monkeys also show a resistance to bar-pressing extinction (Butters et al , 1968, Kirkby et al , 1968, Schmaltz et al , 1972) In view of these data, it appears that partial destruction of the caudate nucleus or neostriatum prevents the disruption of previously established target values, i e links between different responses forming an integrated and precisely timed sequence of spatio-temporal combinations of various muscle contractions, whereas the ability to create completely new target values is unaffected As mentioned above, continuous integration of both extero- and interoceptive information is required for the elicitation or adjustment of the next activity in the ongoing sequence of activities It has been reported that cats and monkeys with subtotal ablation of the caudate nucleus are not impaired in the performance of involuntary movements (Denny-Brown, 1962, Mettler, 1942, 1945, 1967) according to Mettler, the interoceptive information seems to dominate the animal These data indicate that animals without this part of the brain can still make the comparison between the interoceptive information and its target value on the level of involuntary movements, however, Akert et al (1951) using cats and Hansig et al (1968) using rats have found that neostriatal-lesioned animals cannot respond adequately in tactile placing tests If one assumes as a working hypothesis that the integration of incoming signals is affected in neostriatal-lesioned animals, it appears that the integration of both extero- and interoceptive information is affected

There is, in fact, evidence that the caudate nucleus can modify novel inputs according to sensory information previously received (cats Buchwald et al , 1962) In addition, it has been shown that the caudate nucleus can inhibit the activity in motor, sensory and associate cortex on the one hand (Demetrescu et al , 1965, Krauthamer et al , 1965, La Grutta et al , 1969a, b), and inhibit and, in some cases, facilitate the reception of afferent sensory information from auditory and visual receptors on the other hand (Amato et al , 1971,

Buchwald et al , 1961, 1962, Fox et al , 1962, Krauthamer et al , 1967, La Grutta et al , 1969a, b)
These data, together with the fact that the caudate nucleus can be regarded from the anatomical point of view as a relay-station between the sensory input (thalamus), the sensory storage mechanisms (subcortical and cortical structures) and the motor output (caudato-spinal and caudato-cortico-spinal tracts) (see 2 2), indicate that, indeed, the caudate nucleus is able to compare novel inputs with previously established stored information
In view of these considerations, it appears that the available data are compatible with the following concept

> the caudate nucleus forms part of a system in which incoming signals are compared with previously established target values, i e links between two or more responses forming an integrated sequence of elements, normal activation of this system produces a break-down of the established chain of responses, and enables the organism to establish completely new combinations according to available sensory information

In other words, the caudate nucleus contains, or is contained in, a basic system which enables the organism to perform biologically adaptive behavioural responses It is important to realize that both hyperactivation and hypoactivation of this system can elicit a repetition of identical behavioural patterns In the case of hyperactivation, the repetition of specific behavioural elements is completely dependent on the sensory stimulation encountered and the response can change according to changes occuring in sensory information, thus, completely new combinations may also occur In the case of hypoactivation, however, the repetition of behavioural elements is nearly independent of changes occuring in the sensory stimulation encountered during the ongoing activity, in view of these considerations, only hypoactivation can induce perseverative behaviour
The proposed concept has the implication that the nature of the fragments of behavioural patterns induced by activation of the caudate nucleus is completely independent of the functional properties of this nucleus, factors such as species-specific structures in the nervous system, internal state and external situation may be relevant in this respect
The concept of the involvement of the caudate nucleus in comparing incoming signals with previously established target values is not completely new Recently, Potegal has demonstrated that neostriatal-lesioned rats are impaired in the performance of an "absolute spatial discrimination" task (i e locating an object in space by reference to itself), but not in the performance of a "relative spatial discrimination" task (i e locating an object in space without any reference to itself) (Potegal, 1969), from such data and the fact that

patients with Huntington's chorea, having severe degenerations of intracaudate neurons, are impaired in spatial-motor tasks which involve comparison of self-produced movements, Potegal has suggested that the caudate nucleus is involved in a so-called "compensatory updating" mechanism, in which self-produced movements are adjusted according to the internal representation of previously recognized absolute spatial location (Potegal, 1972) Thus, it appears that Potegal has recognized the principle of comparing incoming signals with target values, although he assumes that the target value itself is also stored in this system

> "the caudate nucleus contains or is contained in a system in which potential orientation movements of the head and eyes are the code for spatial location"

6 2 RESPONSE CHAINING SYSTEM AND AMPHETAMINE-INDUCED EFFECTS

6 2 1 THE AMPHETAMINE-INDUCED STEREOTYPIES

It is known that amphetamine which inter alia increases the dopamine activity in the neostriatum (see 2 4 1 2 and 3 1 - 3 3) also induces merely loosened elements which are compulsive in their repetitiveness for instance, pecking in pigeons, sniffing in rats and intention movements in cats (Randrup et al , 1967)

Although it will be clear that other factors cannot be excluded, the idea that amphetamine may also disrupt the normal chain of complex responses, cannot be rejected in fact, it enables us to understand the variability of the amphetamine-induced effects across species It has been found that amphetamine mainly induces species-specific effects in lower animals such as mice, rats, guinea pigs and cats, but only individual-characteristic effects in primates (Randrup et al , 1967)

It is known that a number of complex movements are characteristic for either a species or a higher taxonomic group The form of these movements, i e the relationship between their parts, seems to be independent of environmental stimuli, although the completeness of these patterns can be modified by feedback signals (Tinbergen, 1942, Hinde, 1966) At the extremes, two possibilities are open (a) the target value, i e the links between the different parts of the temporal patterning of the muscular activity, is nearly uninfluenced by practice or example for instance, lateral head movements of human babies in finding the nipple (Prechtl, 1958), and (b) the target value is gradually build up during development

In fact, most complex movements, including skilled movements, are first performed in an incomplete form, and then the development of the chain of responses gradually occurs (Welker, 1964, Hinde, 1966) As the nature of the central nervous system and effector mechanisms limits the degree of complexity of these patterns, species at different phylogenetic levels differ accordingly in their behavioural capacities From this point of view, it is axiomatic that the probability of the appearance of identical responses in different animals of one species decreases inversely with the phylogenetic level when a disruption of *previously* established target values is produced As amphetamine produces mainly species-specific effects in lower animals, but mainly individual-characteristic effects in higher animals, it appears that, indeed, the amphetamine-induced stereotypies may be due to the interference of amphetamine with the mentioned neostriatal function, this is in agreement with neuropharmacological studies which stress the importance of neostriatal dopamine in the amphetamine-induced stereotypies (see 2 4 2) On the basis of the fact that the nature of the fragments of behavioural patterns induced are not determined by the functional properties of the neostriatum, it is quite understandable that manipulation of other brain structures can also modify the amphetamine-induced stereotypies (see 2 4 2)

6 2 2 THE AMPHETAMINE-INDUCED PSYCHOSES

Finally, it is rather intriguing that the present concept may also throw some new light on the relationship between motor and mental disorders The evidence, which is briefly reviewed in 1 1 1 and 1 1 2 , suggests that both motor and mental functioning are associated with the dopamine mechanism in the brain Randrup et al (1972) considering the relevance of anatomical, biochemical, neuropharmalogical and clinical data to this relationship have suggested that a hyperactivity of the nigro-neostriatal, dopamine system is associated with certain psychotic states in man (see also chapters 1 and 2) As excessive activation of the brain dopamine mechanisms by means of chronic intake of dexamphetamine or one of its close analogues produces a schizophrenic-like psychosis, i e a severe disorganization of thought, marked by the appearance of isolated elements which are compulsive in their repetitiveness (Angrist et al , 1970, 1971, Tatetsu et al , cited by Randrup et al , 1967), it is attractive to speculate that the same system as involved in the motor function is affected, i e the system in which incoming signals are compared with previously established "target values" In this context, the "target value" denotes the "should be value" of the interrelationship between different concepts and conceptual frames forming the basis of thinking, problem solving, sensation and perception, i e cognition in its broadest sense (cf the theory of Piaget who pointed out that the development of cognition via processes such as

accomodation and assimilation finally results in so-called schemata (Piaget, cited by Deutsch, 1967)) Accordingly, normal activation of this system may result in a break-down of the previously established target values, i e links between different concepts and conceptual frames, and enable the organism to re-establish completely new combinations according to the sensory information encountered In other words, the same system, which enables the organism to perform biologically adaptive motor responses, also enables the organism to perform adaptive mental responses This is in agreement with the fact that restoration of the decreased dopamine activity in the brain of parkinsonian patients not only improves the motor performance, but also improves intellectual functioning to a certain degree (Marsh, 1971, Meier et al , 1970) it appears that such a restoration induced by L-DOPA gives the organism a greater flexability to respond more adequately to changes occuring in its environment On the other hand, a decrease in the nigro-neostriatal, dopamine activity itself is accompanied by both motor disorders such as rigidity, tremor and hypokinesia and mental disorders such as rigidity in thinking, lack of creativity and disturbances in the so-called "Subjekt-Umwelt" relationship (Barbeau et al , 1965, Calne, 1970, Cooper, 1969, Korten, 1969, Martin, 1967, Riklan et al , 1961) this is also in agreement with the above-mentioned concept that an organism, in which the nigro-neostriatal dopamine system is impaired, cannot disrupt previously established target values, and will show a tendency to perseverate in both motor and mental activities
Although it is difficult to prove that the schizophrenic-like psychoses induced by L-DOPA in parkinsonian patients or by chronic intake of amphetamine-like compounds consist of merely loosened elements, or of completely new combinations of these elements, the induced psychological changes often described as "loosening of ego-structure", "dissolving of ego-boundaries" and "disrupting of ego-defenses" on the one hand (Mandell et al , 1967) and as "auditory and visual hallucinations in a setting of clear consciousness" on the other hand (Angrist et al , 1970, Connell, 1958) point in this direction As the questions which are raised by such psychological disorders must be considered by psychiatrists and psychologists, it will be clear that further evaluation of the mentioned speculation cannot be given in this study However, it is worth mentioning that it fits in very well with the hypothesis of the ontogeny of endogeneous psychoses as formulated by Ploog (1957, 1958, 1969)

> "In den experimentellen Psychosen entsteht eine Dissolution der Stimmungshierarchy In unserer verhaltensbiologischen Terminologie bedeutet Dissolution dementsprechend eine Desintegration der Stimmungshierarchy mit dem Effekt, dass der Verlust an Handlungsfreiheit ein dominierendes Hervortreten von Partialstimmungen nach sich sieht Dies fuhrt zu einem Anpassungsmangel und zu vergleichsweise starreren (automatischen) Handlungsablaufen" — "Wir haben diesen

Abbau des Verhalten im Paralelle zu den motorischen Stereotypien und zu den motorischen Schablonen in zerebralorganischen Abbau gesetzt, um auf niederer funktionsebene dasselbe Prinzip aufzuzeigen, namlich den Verlust an Freiheitsgraden der Bewegung beigleichzeitigen Hervortreten angeborenen Bausteine des Verhaltens, die wir normalerweise nur in der Sauglingsmotorik sehen"

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SUMMARY

The aim of this thesis was to study the role of intracaudate dopamine and serotonin in the neurochemical control of behaviour.

Chapter 1 is a general introduction to the subject of this thesis. In the first part of this chapter, the rationale for extending our knowledge in this field is given. As both L-3,4-dihydroxyphenylalanine, having a limited effectiveness in the treatment of the Parkinson's disease, and neuroleptics, having a limited effectiveness in the treatment of certain schizophrenic-like psychoses, interfere with the brain dopamine mechanisms, it is axiomatic that detailed knowledge of the dopamine-richest structure in the brain, i.e. the caudate nucleus, may contribute to the development of a more successful approach to the pharmacological treatment of these psychomotor diseases. In the last part of this chapter, the rationale for the target structure, i.e. the caudate nucleus of cats, and the method employed, i.e. direct chemical stimulation of intracaudate structures, is given.

Chapter 2 is a selective survey of data from the literature pertaining to the caudate nucleus of cats. In the first section of this chapter, the role of the caudate nucleus in the regulation of behavioural activities is considered. This survey reveals that the caudate nucleus not only functions as a part of a pure motor system regulating posture and simple movements, but also as a part of a system regulating highly complex behavioural activities. In the next section of this chapter, the anatomical aspects of the caudate nucleus in cats are discussed. The reviewed data show that the caudate nucleus forms part of a large number of closed circuits indicating that it may function on a relatively high level of integration. Furthermore, it appears that it is nearly impossible to analyse the anatomical-physiological basis of the caudate functions by means of classical methods such as electrical stimulation or electrocoagulation because of the highly complex anatomical and neurophysiological properties of this nucleus. In the third section of this chapter, attention is paid to the putative neurotransmitter role of dopamine, acetycholine and serotonin. A survey of data from the literature concerning the histochemical distribution and neuropharmacological properties of these compounds shows that all three mentioned substances can be considered as possible neurotransmitters in the caudate nucleus of cats. Furthermore, it becomes clear that dopamine and serotonin, in contrast to acetylcholine, are restricted to nerve terminals originating from distinct, afferent, caudate fibre systems. In the final section of this chapter, the role of neostriatal dopamine and serotonin in the behaviour of rats is considered. This survey reveals that studies dealing exclusively with the role of neostriatal dopamine in the normal behaviour of rats have

produced a number of conflicting data, whereas studies dealing with its role in syndromes elicited by compounds, which probably interfere with neostriatal dopamine activity, have shown that it might play a role in the elicitation of the so-called dexamphetamine, apomorphine, or neuroleptic syndromes, studies dealing with the role of serotonin in the normal behaviour of rats have only shown that there are serotonin-sensitive sites within the neostriatum However, studies concerning exclusively the role of caudate dopamine and serotonin in behaviour of other mammals are completely lacking

Chapter 3, 4 and 5 deal with experimental studies in which the role of caudate dopamine and serotonin in the behaviour of cats is analysed For the results reached with respect to specific topics the reader is referred to the abstracts presented at the beginning of each section

Chapter 3 is dedicated to individual studies dealing with the role of intracaudate dopamine in the behaviour of cats In the first section, a description of the behavioural effects evoked by local application of dopamine and related compounds is given Attention is directed to the influence of different doses and to the sensitivity of different areas In the next section, the chemical specificity of the effects described in the first section of this chapter is considered Moreover, attention is paid to the usefulness of this "model" for testing substances which are believed to interfere with dopamine-sensitive sites In the third section, a clinical description of some behavioural responses evoked by dopamine and related compounds is given Possible implications for the treatment of certain psychomotor diseases in man are discussed In the final section of this chapter, an effort is made to determine whether facilitating or inhibiting processes are involved in the elicitation of the dopamine-induced effects, for this purpose, an analysis of the relation between chemically and electrically evoked responses is made

Chapter 4 is dedicated to two individual studies dealing with the role of intracaudate serotonin in the behaviour of cats In the first section, an analysis of the behavioural effects induced by local application of serotonin, dexamphetamine and related compounds is made In the last section, an effort is made to determine whether facilitating or inhibiting processes are involved in the elicitation of the serotonin-induced effects, for this purpose too, an analysis of the relation between chemically and electrically evoked responses is made

Chapter 5 is dedicated to studies dealing with the transneuronal relationship between the dopamine-sensitive and serotonin-sensitive areas in the caudate nucleus of cats A possible way by which the dopamine, acetylcholine and serotonin mechanisms might operate is proposed

Chapter 6 is devoted to the question of whether the results obtained contribute to a better understanding of the functional properties of the caudate nucleus In this chapter, the separate lines of evidence discussed in chapter 2, together with the results of the investigations presented in chapter 3, are put together into a single coherent interpretation It is suggested that "normal activation of the caudate nucleus, which forms a part of a system in which incoming signals are compared with previously established target values, i e links between two or more responses forming an integrated sequence of elements, produces a break-down of previously established chains of responses, and enables the organism to establish completely new combinations according to available sensory information ' In other words, it is suggested that the caudate nucleus contains, or is contained in, a basic system which enables the organism to perform biologically adaptive behavioural responses Apart from the fact that this concept contributes to a better understanding of the dexamphetamine-induced stereotypies, it also opens a new direction in which one may look for a more fundamental understanding of certain functional and experimental schizophrenic-like psychoses

CURRICULUM VITAE

Alexander Rudolf Cools werd geboren op 14 september 1941 te Den Haag Hij bezocht het Aloysius college aldaar en het Canisius college te Nijmegen, alwaar hij het diploma gymnasium β in juni 1961 behaalde Hij liet zich in 1962 inschrijven als student biologie aan de Katholieke Universiteit te Nijmegen, waar hij in oktober 1966 het kandidaats- en in juni 1969 cum laude het doktoraalexamen aflegde, met als hoofdvak chemische cytologie en als bijvakken psychofarmakologie, genetika en zoologie (ethologie) — voor welk laatste vak hij de Gemeentelijke Universiteit te Amsterdam van september 1967 tot maart 1968 bezocht In augustus 1969 werd hij wetenschappelijk ambtenaar aan de Fakulteit der Wiskunde en Natuurwetenschappen van de Katholieke Universiteit te Nijmegen onder gezag van Prof Dr J M van Rossum ten behoeve van de afdeling Farmakologie onder leiding van Prof Dr E J Ariens Een stipendium van de 'European Training Program in Brain and Behaviour Research" stelde hem in staat zich van september 1971 tot januari 1972 te bekwamen in de neurobiologie aan het Max Planck Instituut voor Psychiatrie te Munchen onder leiding van Prof Dr D Ploog Sinds 1969 is hij gehuwd

Pul	Pulvinar
Put	Putamen
PVA	N periventricularis anterior
R	N reticularis
RM	N ruber, divisio magnocellularis
RP	N ruber, divisio parvocellularis
RPO	Regio praeoptica
S	Stria medullaris
SCh	N supra chiasmaticus
SNC	Substantia nigra, divisio compacta
SNR	Substantia nigra, divisio reticulata
SO	N supraopticus
Spt	Area septalis
ST	Stria terminalis
STh(SU)	N subthalamicus
SU(STh)	N subthalamicus
TMT	tractus mammillo-thalamicus
TO	tractus opticus
tt	taenia tecta
VA	N ventralis anterior thalami
VL	N ventralis lateralis thalami
VMH	N ventromedialis hypothalami
VPL	N ventralis postero-lateralis thalami
VPM	N ventralis postero-medialis thalami
ZI	Zona incerta

LITERATURE

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APPENDIX key to anatomical abbreviations used in chapters 3, 4 and 5

Aa	Area amygdaloidea anterior
Abm	N amygdaloideus basalis, divisio magnocellularis
Abp	N amygdaloideus basalis, divisio parvocellularis
Ac	N amygadaloideus centralis
Acb	N accumbens
CA	commissura anterior
CC	corpus callosum
Cd	N caudatus
Ch	chiasma opticum
Ci	capsula interna
CL(Cl)	N centrolateralis thalami
cc	Claustrum
Cm(NCM)	N centromedialis thalami
Cm	N centrum medianum thalami
EN	N entopeduncularis
FCd	fundus caudati
fsc	fasciculus subcallosum
Fx	fornix
GL	corpus geniculatum laterale
GP	Globus pallidus
H_1,H_2	Forel's fields
HL	Hypothalamus lateralis
Hp	Hypothalamus posterior
IO	Oliva inferior
IV	N interventricularis
LC	N raphe linearis, central part
LD	N lateralis dorsalis thalami
LME	Lamina medullaris externa
LP	N lateralis posterior thalami
LR	N raphe linearis, rostral part
MD	N medialis dorsalis thalami
MRF	formatio reticularis mesencephali
MI	N mammilaris lateralis
Mm	Corpus mammilare
NCM(Cm)	N centromedialis thalami
NPr	N prothalamicus
OT	tectum opticum
Pc	N paracentralis thalami
Ped	Pedunculus cerebralis
Pf	N paracentralis thalami
Pir	lobus piriformis

STELLINGEN

I

De bewering, dat het cirkelgedrag van ratten na een unilaterale lesie van het neostriatum een bruikbaar model is voor het ophelderen van het werkingsmechanisme van stoffen, die mogelijk de dopamine neurotransmissie beinvloeden, houdt geen stand

Andén, N E, Dahlstrom, A, Fuxe, K and Larsson, K Acta Pharmacol Toxicol 24, 263 (1966)
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Dit proefschrift

II

Het geringe verschil in het psychotogene effekt van d-amfetamine versus l-amfetamine steunt de hypothese betreffende de rol van de nucleus caudatus in de aetiologie van bepaalde psychoses.

Angrist, B and Gershon, S Pharmakopychiatr Neuro-Psychoparmakol 4, 63 (1971)
Dit proefschrift

III

Het lijkt aannemelijk, dat de neurologische muizenmutant Varitint-Waddler een bruikbaar model is voor het verschaffen van een beter inzicht in de bij de mens voorkomende kombinatie van stoornissen in het bewegingsapparaat, afwijkingen in de pigmentatie van de huid en het optreden van psychoses

Cools, A R Psychopharmacologia 24, 384 (1972)

IV

Alvorens psychofarmaka aan de Geneesmiddelen Commissie ter beoordeling voorgedragen worden, dient bestudeerd te zijn of en in hoeverre deze potentiele geneesmiddelen het sociale gedrag beinvloeden.

V

Afgezien van het feit dat neurobiologie behoort te zijn opgenomen in het studie-programma van pre-kandidaten in de biologie, verdient het ten sterkste aanbeveling neurobiologie als volwaardige afstudeerrichting in de biologie te erkennen.

VI

Het huidige subsidie-beleid van de Nederlandse Organisatie voor Zuiver-Wetenschappelijk Onderzoek versterkt in toenemende mate de neiging zich tot het analyseren van detail-problemen te beperken

VII

Het trekken van politieke en sociale konsekwenties uit de - op basis van het biometrische model $P = G + E$ gemaakte - schatting, dat ca 80% van de totale variantie in intelligentie in een moderne, Westerse, blanke, populatie aan de invloed van erfelijkheid moet worden toegeschreven, kan niet toelaatbaar geacht worden

Selectie voor en in het hoger onderwijs Een probleemanalyse Staatsuitgeverij, 's-Gravenhage (1972)

VIII

Het plukken van wilde bloemen omwille van hun schoonheid is een kenmerkende uiting van Westerse hebzucht

Nijmegen, 20 juni 1973 A R Cools